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INF-TEC-2025 12

Tecentriq®

Atezolizumab

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Antineoplastic agent, humanized immunoglobulin G1 (IgG1) monoclonal antibody.
ATC Code – L01FF05

1.2 TYPE OF DOSAGE FORM

- Intravenous (IV) formulation: Concentrate for solution for infusion.
- Subcutaneous (SC) formulation: Solution for injection

1.3 ROUTE OF ADMINISTRATION

Intravenous (IV) Infusion.
Subcutaneous (SC) injection

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile Product.

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: atezolizumab
Tecentriq IV
Tecentriq solution for intravenous (IV) infusion is supplied as single-use vials containing preservative-free, colorless to slightly yellow solution, at an active ingredient concentration of 60mg/mL, as follows:

- 14 mL vial containing a total of 840 mg atezolizumab
- 20 mL vial containing a total of 1,200 mg atezolizumab

Excipients: L-histidine, glacial acetic acid, sucrose, polysorbate 20 and water for injection.

Tecentriq SC
Tecentriq solution for subcutaneous (SC) injection is supplied as sterile ready-to-use single-dose vials containing preservative-free, colorless to slightly yellow solution, at an active ingredient concentration of 125 mg/mL, as follows:

- 15 mL containing a total of 1875 mg of atezolizumab.

Tecentriq SC contains recombinant human hyaluronidase (rHuPH20) at a concentration of 2,000 U/mL, an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously.

Excipients: rHuPH20, L-Histidine, acetic acid 30%, sucrose, polysorbate 20, L-methionine and water for injection.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

Tecentriq IV and Tecentriq SC
Early-stage non-small cell lung cancer
Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection for adult patients with Stage II to IIIA (7th edition of the UICC/AJCC-staging system) non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and whose disease has not progressed following platinum-based adjuvant chemotherapy (see Section 3.1.2 Clinical / Efficacy Studies).

Metastatic non-small cell lung cancer
Tecentriq, in combination with Avastin, paclitaxel and carboplatin, is indicated for the treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC) who had not received prior chemotherapy.

Tecentriq as monotherapy is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy.
Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving Tecentriq.

Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for first-line treatment of patients with metastatic non-squamous NSCLC who do not have EGFR or ALK genomic tumor aberrations.

Tecentriq as monotherapy is indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have a PD-L1 expression ≥ 50% tumor cells (TC) or ≥ 10% tumor-infiltrating immune cells (IC) and who do not have EGFR or ALK genomic tumor aberrations

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with NSCLC who are ineligible for platinum-based chemotherapy and who do not have EGFR or ALK genomic tumor aberrations, who have:
- locally advanced, unresectable NSCLC not amenable for definitive chemoradiotherapy, or
- metastatic NSCLC (see section 3.1.2 Clinical / Efficacy Studies).

Small cell lung cancer
Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).

Triple-negative breast cancer
Tecentriq, in combination with nab-paclitaxel, is indicated for the treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors have PD-L1 expression of ≥1% on IC, and who have not received prior chemotherapy for metastatic disease.

Hepatocellular carcinoma
Tecentriq, in combination with Avastin, is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

2.2 DOSAGE AND ADMINISTRATION

General

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Tecentriq must be administered under the supervision of a qualified healthcare professional.

It is important to check the product labels to ensure that the correct formulation (Tecentriq IV or Tecentriq SC) is being administered to the patient as prescribed.

Patients currently receiving Tecentriq IV can switch to Tecentriq SC (or vice versa).

The safety and efficacy of alternating or switching between Tecentriq and products that are biosimilar but not deemed interchangeable to Tecentriq has not been established. Therefore, the benefit/risk of alternating or switching need to be carefully considered.

Tecentriq IV
Tecentriq IV formulation is not intended for subcutaneous administration.

Tecentriq IV formulation must be administered as an intravenous infusion. Do not administer as an IV push or bolus.

Do not co-administer other medicinal products through the same infusion line.
The initial dose of Tecentriq must be administered over 60 minutes. If the first infusion is tolerated all subsequent infusions may be administered over 30 minutes.

Tecentriq SC
Tecentriq SC formulation is not intended for intravenous administration.

Tecentriq SC must be administered as a subcutaneous injection only (see section 4.2 Special Instructions for Use, Handling and Disposal). Prior to administration, remove Tecentriq SC from refrigeration and allow the solution to reach room temperature.

Administer 15 mL of Tecentriq SC solution subcutaneously in the thigh in approximately 7 minutes. Use of a SC infusion set (e.g. winged / butterfly) is recommended. DO NOT administer the remaining residual hold-up volume in the tubing to the patient.

The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5 cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with Tecentriq SC, other medications for subcutaneous administration should preferably be injected at different sites

Patient Selection
If specified in the indication, adult patients should be selected for treatment based on the tumor expression of PD-L1 confirmed by a validated test (see section 3.1.2 Clinical / Efficacy Studies)

Table 1 Recommended dose for Tecentriq monotherapy by intravenous (IV) infusion or subcutaneous (SC) injection

Indication	Recommended dose and schedule	Duration of treatment (see section 3.1.2 Clinical / Efficacy Studies)
1L and 2L NSCLC	Tecentriq IV • 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks OR Tecentriq SC 1875 mg every 3 weeks	Until loss of clinical benefit or unacceptable toxicity
Early-stage NSCLC		For 1 year unless disease recurrence or unacceptable toxicity.

Table 2 Recommended dose for Tecentriq combination therapy by intravenous (IV) infusion or subcutaneous (SC) injection

Indication	Recommended dose and schedule		Duration of treatment
	Tecentriq	**Combination medicinal products**	(see section 3.1.2 Clinical / Efficacy Studies)
1L non-squamous metastatic NSCLC: Tecentriq with Avastin, paclitaxel, and carboplatin	Induction and maintenance phases: Tecentriq IV • 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks OR Tecentriq SC 1875 mg every 3 weeks Tecentriq should be administered first when given on the same day.	Induction phase (four or six cycles): • Avastin, paclitaxel, and then carboplatin are administered every 3 weeks. Maintenance phase • Avastin is administered every 3 weeks.	Until loss of clinical benefit or unacceptable toxicity.
1L non-squamous metastatic NSCLC: Tecentriq with nab-paclitaxel and carboplatin		Induction Phase (four or six cycles): • Nab-paclitaxel and carboplatin are administered every 3 weeks. • For each 21-day cycle, nab-paclitaxel and carboplatin are administered on day 1. • In addition, nab-paclitaxel is administered on days 8 and 15.	
1L ES-SCLC: Tecentriq with carboplatin and etoposide		Induction Phase: (four cycles) • Carboplatin and etoposide are administered by IV infusion every three weeks. • Carboplatin and etoposide are administered on day 1 of each cycle, and etoposide is also administered on days 2 and 3.	
1L unresectable locally advanced or metastatic TNBC Tecentriq with nab-paclitaxel	Tecentriq IV • 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks OR Tecentriq SC 1875 mg every 3 weeks	Tecentriq should be administered prior to nab-paclitaxel when given on the same day. 100 mg/m^2 nab-paclitaxel is administered on days 1, 8 and 15 of each 28-day cycle.	Until disease progression or unacceptable toxicity.
HCC: Tecentriq with Avastin	Tecentriq IV • 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks OR Tecentriq SC 1875 mg every 3 week	Tecentriq should be administered prior to Avastin when given on the same day. Avastin is administered at 15 mg/kg body weight (bw) every 3 weeks.	Until loss of clinical benefit or unacceptable toxicity.

Tecentriq combination therapy
For the use of Tecentriq in combination therapy, please also refer to the full prescribing information for the combination product. Tecentriq should be administered prior to the combination therapy if given on the same day.

Delayed or Missed Doses
If a planned dose of Tecentriq is missed, it should be administered as soon as possible. The schedule of administration should be adjusted to maintain the appropriate interval between doses.

Dose Modifications
No dose reductions of Tecentriq are recommended.

Dose modifications for immune-mediated adverse reactions
Recommendations for specific adverse drug reactions (see sections 2.4.1 Warnings and Precautions, General and 2.6.1 Undesirable Effects, Clinical Trials) are presented in Table 3.

Table 3 Recommended dose modifications for specific Adverse Drug Reactions

Adverse reaction	Severity	Treatment modification
Immune-mediated pneumonitis	Grade 2	Withhold[1]
	Grade 3 or 4	Permanently discontinue
Immune-mediated hepatitis in patients without HCC	Grade 2 (ALT or AST >3 x ULN or blood bilirubin >1.5 x ULN for more than 5-7 days)	Withhold[1]
	Grade 3 or 4 (ALT or AST >5 x ULN or blood bilirubin >3 x ULN)	Permanently discontinue
Immune-mediated hepatitis in patients with HCC	If AST/ALT is within normal limits at baseline and increases to >3 x to ≤10 x ULN If AST/ALT is >1 to ≤3 x ULN at baseline and increases to >5 x to ≤10 x ULN If AST/ALT is >3 x to ≤5 x ULN at baseline and increases to >8 x to ≤10 x ULN	Withhold[1]
	If AST/ALT increases to >10 x ULN or total bilirubin increases to >3 x ULN	Permanently discontinue
Immune-mediated colitis	Grade 2 diarrhea (increase of ≥ 4-6 stools/day over baseline) or colitis	Withhold[1]
	Grade 3 diarrhea (increase of ≥ 7 stools/day over baseline) or colitis	Withhold[1] Initiate IV corticosteroids and convert to oral corticosteroids after improvement
	Grade 4 diarrhea (life threatening; urgent intervention indicated) or colitis	Permanently discontinue
Immune-mediated	Symptomatic	Withhold[2]

hypothyroidism		Initiate thyroid hormone replacement therapy as needed
Immune-mediated hyperthyroidism	Symptomatic	Withhold[2] Initiate anti-thyroid therapy as needed
Immune-mediated adrenal insufficiency	Symptomatic	Withhold[1]
Immune-mediated hypophysitis	Grade 2 or 3	Withhold[1] Hormone replacement should be initiated as needed.
	Grade 4	Permanently discontinue
Immune-mediated type 1 diabetes	For ≥ Grade 3 hyperglycemia (fasting glucose >250 mg/dL)	Withhold[2] Initiate insulin
Immune-mediated meningitis, encephalitis, myasthenic syndrome / myasthenia gravis, Guillain-Barré syndrome	All grades	Permanently discontinue
Immune-mediated myelitis	Grade 2, 3 or 4	Permanently discontinue
Immune-mediated facial paresis	Grade 1 or 2	Withhold[1]
	Grade 3 or 4	Permanently discontinue
Immune-mediated pancreatitis	Grade 2 or 3 ≥ Grade 3 serum amylase or lipase levels increased (> 2 x ULN)	Withhold[1]
	Grade 4 or any grade recurrent pancreatitis	Permanently discontinue
Immune-mediated myocarditis	Grade 2 or above	Permanently discontinue
Immune-mediated myositis	Grade 2 or 3	Withhold[1]
	Grade 4 or grade 3 recurrent myositis	Permanently discontinue
Immune-mediated nephritis	Grade 2 (creatinine level >1.5 – 3 x baseline or >1.5 –3 x ULN)	Withhold[1]
	Grade 3 (creatinine level >3 x baseline or >3 – 6 x ULN) or 4 (creatinine level >6 x ULN)	Permanently discontinue
Immune-mediated pericardial disorders	Grade 1 pericarditis	Withhold[3]
	Grade 2 or above	Permanently discontinue
Infusion related reactions	Grade 1 or 2	Reduce rate of infusion/injection or withhold treatment/pause the injection Premedication with antipyretic and antihistamines may be considered for subsequent doses
	Grade 3 or 4	Permanently discontinue
Haemophagocytic lymphohistiocytosis	Suspected haemophagocytic lymphohistiocytosis[4]	Permanently discontinue
Rash/Severe cutaneous adverse reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[4]	Withhold
	Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[4]	Permanently discontinue

[1] Treatment with corticosteroid therapy (1-2 mg/kg/day prednisone or equivalent) should be initiated. Treatment with Tecentriq may be resumed in patients with complete or partial resolution (Grade 0 to 1) within 12 weeks, and after corticosteroids have been reduced to ≤10 mg/day oral prednisone or equivalent.
[2] Treatment with Tecentriq may be resumed when symptoms are controlled and the patient is clinically stable.
[3] Conduct a detailed cardiac evaluation to determine the etiology and manage appropriately.
[4] Regardless of severity.

For other immune-mediated reactions, based on the type and severity of the reaction, treatment with Tecentriq should be withheld for Grades 2 or 3 immune-mediated adverse reactions and corticosteroid therapy (1-2 mg/kg/day prednisone or equivalent) should be initiated. If symptoms improve to ≤ Grade 1, taper corticosteroids as clinically indicated. Treatment with Tecentriq may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day.

Treatment with Tecentriq should be permanently discontinued for Grade 4 immune-mediated adverse reactions, or when unable to reduce corticosteroid dose to the equivalent of ≤ 10 mg prednisone per day within 12 weeks after onset.

2.2.1 Special Dosage Instructions

Pediatric Use
The safety and efficacy of Tecentriq in children and adolescents below 18 years of age have not been established. (see section 2.5.4 Pediatric Use, and 3.2.5 Pharmacokinetics in Special Populations)

Geriatric Use
Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age (see sections 2.5.5 Geriatric Use, and 3.2.5 Pharmacokinetics in Special Populations).

Renal Impairment
Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with renal impairment (see section 3.2.5 Pharmacokinetics in Special Populations).

Hepatic impairment
Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild or moderate hepatic impairment. There are no data in patients with severe hepatic impairment (see section 3.2.5 Pharmacokinetics in Special Populations).

2.3 CONTRAINDICATIONS

Tecentriq is contraindicated in patients with a known hypersensitivity to atezolizumab or any of the excipients.

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Tecentriq should be used in combination with nab-paclitaxel and not conventional paclitaxel.

Haemophagocytic lymphohistiocytosis
Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, has been reported in patients receiving Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials and 2.6.2 Postmarketing Experience). HLH should be considered when the presentation of cytokine release syndrome is atypical or prolonged. Patients should be monitored for clinical signs and symptoms of HLH. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated pneumonitis
Cases of pneumonitis, including fatal cases, have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials). Patients should be monitored for signs and symptoms of pneumonitis. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated hepatitis
Cases of hepatitis, some leading to fatal outcomes, have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials). Patients should be monitored for signs and symptoms of hepatitis. Monitor aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin prior to and periodically during treatment with Tecentriq. Consider appropriate management of patients with abnormal liver function tests (LFTs) at baseline. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated colitis
Cases of diarrhea or colitis have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials). Patients should be monitored for signs and symptoms of colitis. Refer to section 2.2. Dosage and Administration for recommended dose modifications. The potential complication of gastrointestinal perforation associated with colitis should be taken into consideration.

Immune-mediated endocrinopathies
Hypothyroidism, hyperthyroidism, adrenal insufficiency and type 1 diabetes mellitus, including diabetic ketoacidosis, have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials). Patients should be monitored for clinical signs and symptoms of endocrinopathies. Monitor thyroid function prior to and periodically during treatment with Tecentriq. Consider appropriate management of patients with abnormal thyroid function tests at baseline. Patients with abnormal thyroid function tests who are asymptomatic may receive Tecentriq. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated meningoencephalitis
Meningoencephalitis has been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials). Patients should be monitored for clinical signs and symptoms of meningitis or encephalitis. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated neuropathies
Myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome, which may be life threatening, and facial paresis were observed in patients receiving Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials). Patients should be monitored for symptoms of motor and sensory neuropathy (also see "Immune-Mediated Myocarditis/Myositis/Myasthenia Gravis Overlap Syndrome" in this section). Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated myelitis
Myelitis has been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials and 2.6.2 Postmarketing Experience). Patients should be closely monitored for signs and symptoms that are suggestive of myelitis. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated pancreatitis
Pancreatitis, including increases in serum amylase and lipase levels, has been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials). Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated myocarditis
Myocarditis, including one fatal case, has been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials). Patients should be monitored for signs and symptoms of myocarditis (also see "Immune-Mediated Myocarditis/Myositis/Myasthenia Gravis Overlap Syndrome" in this section). Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated myositis
Cases of myositis, including fatal cases, have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials). Patients should be monitored for signs and symptoms of myositis (also see "Immune-Mediated Myocarditis/Myositis/Myasthenia Gravis Overlap Syndrome" in this section). Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated nephritis
Nephritis has been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials). Patients should be monitored for changes in renal function. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Infusion related reactions
Infusion related reactions (IRRs) have been observed in clinical trials with Tecentriq including anaphylaxis (see section 2.6.1 Undesirable effects, Clinical Trials). Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated severe cutaneous adverse reactions
Immune-mediated severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients receiving Tecentriq. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, Tecentriq should be withheld for Grade 3 skin reactions until recovery to Grade ≤ 1 or permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered (see Section 2.2).

For suspected SCARs, patients should be referred to a specialist for further diagnosis and management. Tecentriq should be withheld for patients with suspected SJS or TEN. For confirmed SJS or TEN, Tecentriq should be permanently discontinued.

Caution should be used when considering the use of Tecentriq in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Immune-mediated pericardial disorders
Pericardial disorders, including pericarditis, pericardial effusion and cardiac tamponade, some leading to fatal outcomes, have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials and 2.6.2 Postmarketing Experience). Patients should be monitored for clinical signs and symptoms of pericardial disorders. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-Mediated Myocarditis/Myositis/Myasthenia Gravis Overlap Syndrome
Cases of an overlap syndrome defined by the concurrent manifestation of any two or all three of the following conditions: myocarditis, myositis, and myasthenia gravis, have been observed in clinical trials or the post-marketing setting with Tecentriq. Onset occurs predominantly within the first two treatment cycles. It is important to recognize overlapping symptoms, which can complicate diagnosis and management and could have a higher risk of mortality. Patients presenting with signs or symptoms of one condition should also be monitored for the other two conditions and should be managed as clinically indicated. Refer to section 2.2. Dosage and Administration for recommended dose modification guidance for the individual conditions (myocarditis, myositis, myasthenia gravis) and adhere to the most stringent recommendations.

Other immune-mediated adverse reactions
Haemolytic anaemia

The following additional clinically significant immune-mediated adverse reactions were reported in less than 1% (unless otherwise indicated) in patients treated with Tecentriq for various cancers and/or reported with use of other PD-1/PD-L1 blocking antibodies: aplastic anemia

The following additional clinically significant, immune-mediated adverse reactions have been reported in clinical studies with Tecentriq: uveitis (see section 2.6.1 Undesirable effects, Clinical Trials). Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Special populations
Patients with autoimmune disease were excluded from clinical trials with Tecentriq. In the absence of data, Tecentriq should be used with caution in patients with autoimmune disease, after assessment of the potential risk-benefit.

Embryofetal toxicity
Based on the mechanism of action, the use of Tecentriq may cause fetal harm. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death.
Pregnant women should be advised of the potential risk to the fetus. Women of childbearing potential should be advised to use highly effective contraception during treatment with Tecentriq and for 5 months after the last dose (see sections 2.5.1 Females and Males of Reproductive Potential, and 3.3.4 Reproductive Toxicity).

Infection
Severe infections have been observed in clinical trials with Tecentriq. Monitor patients for signs and symptoms of infection and treat with antibiotics for suspected or confirmed bacterial infections. Withhold Tecentriq for ≥ Grade 3 infection.

Ocular Inflammatory Toxicity
Ocular inflammatory toxicity has been observed in clinical trials with Tecentriq. Withhold Tecentriq for moderate and permanently discontinue for severe ocular inflammatory toxicity.

2.4.2 Drug Abuse and Dependence

No data to report.

2.4.3 Ability to Drive and Use Machines

No studies on the effects on the ability to drive and to use machines have been performed.

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential

Fertility
Based on animal studies, Tecentriq may impair fertility in females of reproductive potential while receiving treatment (see section 3.3.3 Impairment of Fertility).

Contraception
Female patients of childbearing potential should use highly effective contraception and take active measures to avoid pregnancy while undergoing Tecentriq treatment and for at least 5 months after the last dose (see sections 2.4.1 Warnings and Precautions, General, and 3.3.4 Reproductive Toxicity).

2.5.2 Pregnancy

There are no clinical studies of Tecentriq in pregnant women. Tecentriq is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus (see section 3.3.4 Reproductive Toxicity).

Labor and Delivery
The use of Tecentriq during labor and delivery has not been established.

2.5.3 Lactation

It is not known whether Tecentriq is excreted in human breast milk. No studies have been conducted to assess the impact of Tecentriq on milk production or its presence in breast milk. As the potential for harm to the nursing infant is unknown, a decision must be made to either discontinue breast-feeding or discontinue Tecentriq therapy.

2.5.4 Pediatric Use

Tecentriq is not approved for use in patients under the age of 18 years. The safety and efficacy of Tecentriq in this population has not been established. Tecentriq did not demonstrate clinical benefit in pediatric patients in a clinical trial. (see section 3.2.5 Pharmacokinetics in Special Populations)

2.5.5 Geriatric Use

No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients (see sections 2.2.1 Special Dosage Instructions, and 3.2.5 Pharmacokinetics in Special Populations).

2.5.6 Renal Impairment

See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations.

2.5.7 Hepatic Impairment

See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations.

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Tecentriq in the adjuvant NSCLC setting

The safety profile of atezolizumab in the adjuvant setting in the non-small cell lung cancer (NSCLC) patient population (IMpower010) was generally consistent with the overall pooled monotherapy safety profile in the advanced setting, although some differences were noted. In comparison to the pooled monotherapy population with advanced disease, a higher number of patients receiving atezolizumab in the adjuvant NSCLC study discontinued atezolizumab due to adverse events (AE) (18.2%) and more immune-mediated adverse events (51.7%) were noted. However, there was a lower frequency of Grade 3-4 AEs (21.8%) and serious AEs (17.6%) in patients treated with atezolizumab monotherapy in IMpower010. The most common AEs observed in IMpower010 were cough (13.3%), pyrexia (13.1%), hypothyroidism (11.1%), AST increased/ALT increased (10.7% for both), arthralgia (10.5%), and pruritus (10.3%). The incidence of immune-related adverse reactions of atezolizumab in IMpower010 was 51.7% (all-grade) and 7.9% (Grades 3-4). The most common immune-mediated adverse events in IMpower010 were rash (18.4%), hypothyroidism (17.4%), hepatic laboratory abnormalities (16.4%), and hyperthyroidism (6.5%).

Tecentriq monotherapy

The safety of Tecentriq monotherapy is based on pooled data in 3178 patients who received Tecentriq IV with multiple tumor types, with supporting data from the estimated cumulative exposure in >13000 patients across all clinical trials. Table 4 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Tecentriq IV and SC.

Table 4 Summary of adverse reactions occurring in patients treated with Tecentriq IV and SC monotherapy in clinical trials

ADR (MedDRA)	Tecentriq			
System Organ Class	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency Category (All Grades)
Blood and Lymphatic System Disorders				
Anemia[nn]	515 (16.2%)	163 (5.1%)	0 (0%)	Very Common
Thrombocytopenia[n]	116 (3.7%)	27 (0.8%)	0 (0%)	Common
Haemophagocytic lymphohistiocytosis[ff]	1 (<0.1%)	0 (0%)	1 (<0.1%)	Rare
Neutropenia[mm]	49 (1.5 %)	21 (0.7%)	1 (<0.1%)	Common
Cardiac Disorders				
Myocarditis [a]	-	-	-	Rare
Pericardial disorders[ee,ff]	45 (1.4%)	22 (0.7%)	2 (<0.1%)	Common
Endocrine Disorders				
Hypothyroidism [b]	164 (5.2%)	6 (0.2%)	0 (0%)	Common
Hyperthyroidism [c]	30 (0.9%)	1 (<0.1%)	0 (0%)	Uncommon
Adrenal insufficiency[d]	11 (0.3%)	2 (<0.1%)	0 (0%)	Uncommon
Hypophysitis[y]	2 (<0.1%)	0 (0%)	0 (0%)	Rare
Diabetes mellitus [e]	10 (0.3%)	6 (0.2%)	0 (0%)	Uncommon
Eye Disorders				
Uveitis	3 (<0.1%)	0 (0%)	0 (0%)	Rare
Gastrointestinal Disorders				
Diarrhea[o]	626 (19.7%)	36 (1.1%)	0 (0%)	Very Common
Dysphagia	82 (2.6%)	16 (0.5%)	0 (0%)	Common
Colitis [f]	34 (1.1%)	18 (0.6%)	0 (0%)	Common
Nausea	747 (23.5%)	35 (1.1%)	0 (0%)	Very Common
Vomiting	477 (15.0%)	26 (0.8%)	0 (0%)	Very Common
Abdominal pain	268 (8.4%)	34 (1.1%)	0 (0%)	Common
Pancreatitis [g]	18 (0.6%)	13 (0.4%)	0 (0%)	Uncommon
Oropharyngeal pain [q]	131 (4.1%)	0 (0%)	0 (0%)	Common
Dry mouth	154 (4.8%)	0 (0%)	0 (0%)	Common
General Disorders and Administration Site Conditions				
Chills	207 (6.5%)	2 (< 0.1%)	0 (0%)	Common
Fatigue	1142 (35.9%)	109 (3.4%)	0 (0%)	Very Common
Asthenia	461 (14.5%)	63 (2.0%)	0 (0%)	Very Common
Influenza like illness	186(5.9%)	1 (<0.1%)	0 (0%)	Common
Pyrexia	638 (20.1%)	17 (0.5%)	0 (0%)	Very Common
Injection site reaction [gg]	29 (6.9%)	0 (0%)	0 (0%)	Common
Infections	658 (40.2%)	142 (8.7%)	12 (0.7%)	Very Common
Hepatobiliary Disorders				
ALT increased	167 (5.3%)	46 (1.4%)	0 (0%)	Common
AST increased	180 (5.7%)	46 (1.4%)	0 (0%)	Common
Hepatitis [i]	62 (2.0%)	25 (0.8%)	2 (<0.1%)	Common
Immune System Disorders				
Infusion related reaction [h]	32 (1.0%)	4 (0.1%)	0 (0%)	Common
Hypersensitivity	36 (1.1%)	3 (<0.1%)	0 (0%)	Common
Sarcoidosis [jj]	-	-	-	Very Rare
Infections and Infestations				
Urinary tract infection [p]	368 (11.6%)	86 (2.7%)	0 (0%)	Very Common
Cytomegalovirus infection	1 (< 0.1%)	0 (0%)	0 (0%)	Rare
Investigations				
Gamma-glutamyl transferase increased	35 (1.1%)	19 (0.6%)	0 (0%)	Common
Blood creatine phosphokinase increased	6 (0.2%)	3 (<0.1%)	0 (0%)	Uncommon
Metabolism and Nutrition Disorders				
Decreased appetite	810 (25.5%)	35 (1.1%)	0 (0%)	Very Common
Hypokalemia [v]	142 (4.5%)	33 (1.0%)	0 (0%)	Common
Hyponatremia [w]	171 (5.4%)	98 (3.1%)	0 (0%)	Common
Hypoalbuminemia	114 (3.6%)	10 (0.3%)	0 (0%)	Common
Hyperglycemia	103 (3.2%)	32 (1.0%)	0 (0%)	Common
Hypophosphatemia	77 (2.4%)	22 (0.7%)	0 (0%)	Common
Hypocalcemia	40 (1.3%)	4 (0.1%)	0 (0%)	Common
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	441 (13.9%)	23 (0.7%)	0 (0%)	Very Common
Back pain	487 (15.3%)	52 (1.6%)	0 (0%)	Very Common
Musculoskeletal pain [r]	489 (15.4%)	36 (1.1%)	0 (0%)	Very Common
Arthritis [ll]	64 (2.0%)	8 (0.3%)	0 (0%)	Common
Myositis [t, u]	13 (0.4%)	5 (0.2%)	0	Uncommon
Tenosynovitis [kk]	10 (0.3%)	1 (<0.1%)	0 (0%)	Uncommon
Nervous System Disorders				
Headache	352 (11.1%)	10 (0.3%)	0 (0%)	Very Common
Peripheral neuropathy [ii]	156 (4.9%)	5 (0.2%)	0 (0%)	Common
Guillain-Barré syndrome [j]	5 (0.2%)	4 (0.1%)	0 (0%)	Uncommon
Meningoencephalitis [k]	14 (0.4%)	6 (0.2%)	0 (0%)	Uncommon
Myasthenic syndrome [z]	1 (<0.1%)	0 (0%)	0 (0%)	Rare
Facial paresis[ff]	1 (<0.1%)	0 (0%)	0 (0%)	Rare
Myelitis[ff]	1 (<0.1%)	1 (<0.1%)	0 (0%)	Rare
Renal and Urinary Disorders				
Blood creatinine increased [aa]	171 (5.4%)	14 (0.4%)	0 (0%)	Common
Nephritis [s]	3 (<0.1%)	1 (<0.1%)	0 (0%)	Rare
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	660 (20.8%)	9 (0.3%)	0 (0%)	Very Common
Dyspnea	651 (20.5%)	117 (3.7%)	1 (< 0.1%)	Very Common
Hypoxia [x]	75 (2.4%)	36 (1.1%)	0 (0%)	Common
Pneumonitis [l]	87 (2.7%)	27 (0.8%)	1 (<0.1%)	Common
Nasopharyngitis[bb]	280 (8.8%)	0 (0%)	0 (0%)	Common
Skin and Subcutaneous Tissue Disorders				
Rash [m]	613 (19.3%)	33 (1.0%)	0 (0%)	Very Common
Pruritus	400 (12.6%)	7 (0.2%)	0 (0%)	Very Common
Dry Skin [hh]	199 (6.3%)	2 (<0.1%)	0 (0%)	Common
Psoriatic conditions [cc]	19 (0.6%)	2 (<0.1%)	0 (0%)	Uncommon
Severe cutaneous adverse reactions [dd]	22 (0.7%)	3 (<0.1%)	1 (<0.1%)	Uncommon
Vascular Disorders				
Hypotension	102 (3.2%)	20 (0.6%)	0 (0%)	Common
Eye Disorders				
Ocular inflammatory toxicity	9 (0.6%)	4 (0.2%)	0 (0%)	Uncommon

[a] Reported in studies outside the pooled dataset. The frequency is based on the program-wide exposure. Includes reports of autoimmune myocarditis, immune-mediated myocarditis.

[b] Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, blood thyroid stimulating hormone decreased, autoimmune thyroiditis (cases of autoimmune thyroiditis have been reported in studies outside the pooled dataset), thyroiditis, autoimmune hypothyroidism, euthyroid sick syndrome, myxoedema, thyroid function test abnormal, thyroiditis acute, thyroxine decreased

[c] Includes reports of hyperthyroidism, Basedow's disease, endocrine ophthalmopathy, exophthalmos

[d] Includes report of adrenal insufficiency, primary adrenal insufficiency

[e] Includes reports of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis and ketoacidosis

[f] Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, colitis ulcerative, immune-mediated enterocolitis (cases of immune-mediated enterocolitis have been reported in studies outside the pooled dataset)

[g] Includes reports of pancreatitis, autoimmune pancreatitis, pancreatitis acute, lipase increased and amylase increased

[h] Includes infusion related reaction, cytokine release syndrome and anaphylaxis (anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock), where anaphylaxis was reported outside the pooled dataset.

[i] Includes reports of ascites, autoimmune hepatitis, hepatocellular injury, hepatitis, hepatitis acute, hepatotoxicity, liver disorder, drug-induced liver injury, hepatic failure, hepatic steatosis, hepatic lesion, esophageal varices hemorrhage, varices esophageal

[j] Includes reports of Guillain-Barre syndrome and demyelinating polyneuropathy

[k] Includes reports of encephalitis, meningitis, photophobia

[l] Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis

[m] Includes reports of rash, rash maculo-papular, erythema, rash pruritic, dermatitis acneiform, eczema, dermatitis, rash erythematous, skin ulcer, rash papular, folliculitis, rash macular, skin exfoliation, rash pustular, furuncle, acne, drug eruption,palmar-plantar erythrodysaesthesia syndrome, seborrhoeic dermatitis, dermatitis allergic, erythema of eyelid, skin toxicity, eyelid rash, fixed eruption, rash papulosquamous, rash vesicular, blister, lip blister, pemphigoid, oral blood blister, scrotal dermatitis (cases of scrotal dermatitis have been reported in studies outside pooled dataset)

[n] Includes reports of immune thrombocytopenia (reported in studies outside the pooled dataset), thrombocytopenia and platelet count decreased

[o] Includes reports of diarrhea, frequent bowel movements, and gastrointestinal hypermotility

[p] Includes reports of urinary tract infection, cystitis, pyelonephritis, Escherichia urinary tract infection, pyelonephritis acute, urinary tract infection bacterial, kidney infection, urinary tract infection fungal, urinary tract infection pseudomonal

[q] Includes reports of oropharyngeal pain, throat irritation, oropharyngeal discomfort

[r] Includes reports of musculoskeletal pain,myalgia, bone pain

[s] Includes reports of nephritis and Henoch-Schonlein Purpura nephritis

[t] Includes reports of myositis, rhabdomyolysis, polymyalgia rheumatica, dermatomyositis, muscle abscess, myoglobin urine present

[u] Fatal cases have been reported in studies outside the pooled dataset

[v] Includes reports of hypokalaemia and blood potassium decreased

[w] Includes reports of hyponatraemia and blood sodium decreased

[x] Includes reports of hypoxia, oxygen saturation decreased, PO_2 decreased

[y] Includes reports of hypophysitis and temperature regulation disorder

[z] Includes report of myasthenia gravis

[aa] Includes reports of blood creatinine increased and hypercreatininaemia

[bb] Includes reports of nasopharyngitis, nasal congestion and rhinorrhea

[cc] Includes reports of dermatitis psoriasiform and psoriasis

[dd] Includes reports of dermatitis bullous, exfoliative rash, erythema multiforme, dermatitis exfoliative generalised, toxic skin eruption, toxic epidermal necrolysis

[ee] Includes reports of pericarditis, pericardial effusion, cardiac tamponade and pericarditis constrictive

[ff] Reported from postmarketing experience outside the pooled dataset. The frequency is based on the program-wide exposure.

[gg] Reported in studies outside the pooled dataset (subcutaneous administration related). The frequency is based on exposure to Tecentriq SC in IMscin001 (n=11/247; 4.5%) and in IMscin002 (n=18/175; 10.3%, patients received both Tecentriq SC and IV) and includes reports of injection site reaction, injection site pain, injection site erythema, and injection site rash

[hh] Includes reports of dry skin, xerosis.

[ii] Includes reports of neuropathy peripheral, peripheral sensory neuropathy, polyneuropathy, peripheral motor neuropathy, toxic neuropathy, peripheral sensorimotor neuropathy, autoimmune neuropathy, axonal neuropathy, brachial plexopathy, lumbosacral plexopathy, neuralgic amyotrophy, and neuritis.

[jj] Reported in studies outside the pooled dataset. The frequency is based on the program-wide exposure.

[kk] Includes reports of tenosynovitis, tendonitis, tendon pain and synovitis.

[ll] Includes reports of joint swelling, osteoarthritis, spinal osteoarthritis, polyarthritis, rheumatoid arthritis, joint effusion, spondylitis, autoimmune arthritis, arthropathy, immune-mediated arthritis and rheumatic disorder.

[mm] Includes reports of neutropenia, febrile neutropenia, neutrophil count decreased, neutropenic sepsis.

[nn] Includes reports of anemia, hemoglobin decreased, and red blood cell count decreased.

[oo] The dataset is based on pooled data from studies PCD, FIR, BIRCH, POPLAR, OAK, IMvigor210, IMvigor211, and IMmotion150 (arm B).

Tecentriq combination therapy

Additional ADRs identified in clinical trials (not reported in monotherapy trials) associated with the use of Tecentriq in combination therapy across multiple indications are summarized in Table 5. ADRs with a clinically relevant difference when compared to monotherapy (refer to Table 4) are also presented.

Table 5: Summary of adverse reactions occurring in patients treated with Tecentriq combination therapy in clinical trials

ADR (MedDRA)	Tecentriq + Combination Treatments (n = 4371)			
System Organ Class	All Grades (%)	Grade 3-4 (%)	Grade 5 (%)	Frequency (All Grades)
Blood and Lymphatic System Disorders				
Anemia[*,r]	1622 (37.1%)	637 (14.6%)	0 (0%)	Very Common
Lymphopenia[*, k]	145 (3.3%)	63 (1.4%)	0 (0%)	Common
Neutropenia[*,a]	1565 (35.8%)	1070 (24.5%)	6 (0.1%)	Very Common
Thrombocytopenia[*,‡, b]	1211 (27.7%)	479 (11.0%)	1 (<0.1%)	Very Common
Leukopenia[*, i]	571 (13.1%)	245 (5.6%)	0 (0%)	Very Common
Endocrine Disorders				
Hypothyroidism[*,‡,c]	586 (13.4)	9 (0.2%)	0 (0%)	Very Common
Hyperthyroidism[‡]	193 (4.4%)	7 (0.2%)	0 (0%)	Common
Adrenal insufficiency[‡,d]	40 (0.9%)	8 (0.2%)	1 (<0.1%)	Uncommon
Hypophysitis[‡,e]	13 (0.3%)	5 (0.1%)	0 (0%)	Uncommon
Eye Disorders				
Uveitis[q]	2 (<0.1%)	0 (0%)	0 (0%)	Rare
Gastrointestinal Disorders				
Constipation[*]	1123 (25.7%)	24 (0.5%)	0 (0%)	Very Common
Stomatitis[*]	351 (8.0%)	23 (0.5%)	0 (0%)	Common
General Disorders and Administration Site Conditions				
Oedema Peripheral*	451 (10.3%)	11 (0.3%)	0 (0%)	Very Common
Infections and Infestations				
Lung infection[*,h]	564 (12.9%)	226 (5.2%)	26 (0.6%)	Very Common
Investigations				
Blood alkaline phosphatase increased	200 (4.6%)	26 (0.6%)	0 (0%)	Common
Metabolism and Nutrition Disorders				
Hypomagnesemia[*, j]	403 (9.2%)	22 (0.5%)	0 (0%)	Common
Nervous System Disorders				
Dizziness[*]	408 (9.3%)	9 (0.2%)	0 (0%)	Common
Dysgeusia[*]	269 (6.2%)	0 (0.0%)	0 (0%)	Common
Peripheral neuropathy[*,f]	976 (22.3%)	104 (2.4%)	0 (0%)	Very Common
Syncope[*]	68 (1.6%)	36 (0.8%)	0 (0%)	Common
Renal and Urinary Disorders				
Nephritis[‡, l]	23 (0.5%)	15 (0.3%)	0 (0%)	Uncommon
Proteinuria[*,g]	359 (8.2%)	61 (1.4%)	0 (0%)	Common
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia[*]	236 (5.4%)	4 (< 0.1%)	0 (0%)	Common
Nasopharyngitis[o]	442 (10.1%)	1 (< 0.1%)	0 (0%)	Very Common
Skin and Subcutaneous Tissue Disorders				
Alopecia [n]	1152 (26.4%)	3 (< 0.1%)	0 (0%)	Very Common
Severe cutaneous adverse reactions [p]	27 (0.6 %)	8 (0.2 %)	0 (0%)	Uncommon
Vascular Disorders				
Hypertension[*, m]	611 (14.0%)	258 (5.9%)	0 (0%)	Very Common

[*] ADR occurring at a frequency difference of ≥5% (All grades) or ≥2% (Grades 3-4) compared to the control arm

[‡] Observed rate in the combination represents a clinically relevant difference in comparison to Tecentriq monotherapy

a. Includes reports of neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis and granulocytopenia

b. Includes reports of immune thrombocytopenia, thrombocytopenia and platelet count decreased

c. Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, blood thyroid stimulating hormone decreased, autoimmune thyroiditis, goitre, thyroiditis, thyroxine free decreased, tri−iodothyronine free decreased, thyroid disorder, thyroxine free increased, thyroxine increased, tri−iodothyronine decreased, tri-iodothyronine free increased, blood thyroid stimulating hormone abnormal, euthyroid sick syndrome, myxoedema coma, thyroid function test abnormal, thyroxine decreased, tri-iodothyronine abnormal, silent thyroiditis and thyroiditis chronic

d. Includes reports of adrenal insufficiency, cortisol decreased, adrenocortical insufficiency acute, secondary adrenocortical insufficiency, adrenocorticotropic hormone stimulation test abnormal, Addison's disease, adrenalitis and adrenocorticotropic hormone deficiency

e. Includes reports of hypophysitis, hypopituitarism and temperature regulation disorder

f. Includes reports of neuropathy peripheral, peripheral sensory neuropathy, polyneuropathy, peripheral motor neuropathy, toxic neuropathy, autoimmune neuropathy, neuralgic amyotrophy, peripheral sensorimotor neuropathy, axonal neuropathy, brachial plexopathy, lumbosacral plexopathy and neuritis.

g. Includes reports of proteinuria, protein urine present, haemoglobinuria, nephrotic syndrome, urine abnormality and albuminuria

h. Includes reports of pneumonia, bronchitis, lower respiratory tract infection, tracheobronchitis, infective exacerbation of chronic obstructive airways disease, infectious pleural effusion, paracancerous pneumonia, atypical pneumonia, lung abscess, pleural infection and pyopneumothorax

i. Includes reports of white blood cell count decreased and leukopenia

j. Includes reports of hypomagnesaemia and blood magnesium decreased

k. Includes reports of lymphopenia and lymphocyte count decreased

l. Includes reports of nephritis, tubulointerstitial nephritis, autoimmune nephritis, nephritis allergic, glomerulonephritis, nephrotic syndrome and mesangioproliferative glomerulonephritis

m. Includes reports of hypertension, blood pressure increased, hypertensive crisis, blood pressure systolic increased, diastolic hypertension, blood pressure inadequately controlled and retinopathy hypertensive

n. Includes reports of alopecia, madarosis, alopecia areata, alopecia totalis and hypotrichosis

o. Includes reports of nasopharyngitis, nasal congestion and rhinorrhoea

p. Includes reports of dermatitis bullous, exfoliative rash, erythema multiforme, dermatitis exfoliative generalised, toxic skin eruption, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), and cutaneous vasculitis (cases of SJS and DRESS have been reported in studies outside the pooled dataset).

q. Includes reports of uveitis and iritis

r. Includes reports of anemia, hemoglobin decreased, and red blood cell count decreased

Additional information for selected adverse reactions

The data below reflect information for significant adverse reactions for Tecentriq monotherapy. Details for the significant adverse reactions for Tecentriq when given in combination are presented if clinically relevant differences were noted in comparison to Tecentriq monotherapy. See section 2.4.1 Warnings and Precautions, General for management of the following:

Haemophagocytic lymphohistiocytosis

Haemophagocytic lymphohistiocytosis (HLH) occurred in <0.1% (1/3178) of patients who received Tecentriq monotherapy. The time to onset was 1.6 months. The duration was 1.4 months. HLH led to discontinuation of Tecentriq in 1 (<0.1%) patient. The patient did not require the use of corticosteroids.

Immune-mediated pneumonitis

Pneumonitis occurred in 2.7% (87/3178) of patients who received Tecentriq monotherapy. Of the 87 patients, one event was fatal. The median time to onset was 3.4 months (range: 0.1 to 24.8 months). The median duration was 1.4 months (range 0 to 21.2+ months; + denotes a censored value). Pneumonitis led to discontinuation of Tecentriq in 12 (0.4%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.6% (51/3178) of patients receiving Tecentriq.

Immune-mediated hepatitis

Hepatitis occurred in 2.0% (62/3178) of patients who received Tecentriq monotherapy. Of the 62 patients, two events were fatal. The median time to onset was 1.5 months (range 0.2 to 18.8 months). The median duration was 2.1 months (range 0 to 22.0+ months; + denotes a censored value). Hepatitis led to discontinuation of Tecentriq in 6 (0.2%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.6% (18/3178) of patients receiving Tecentriq.

Immune-mediated colitis

Colitis occurred in 1.1% (34/3178) of patients who received Tecentriq. The median time to onset was 4.7 months (range 0.5 to 17.2 months). The median duration was 1.2 months (range: 0.1 to 17.8+ months; + denotes a censored value). Colitis led to discontinuation of Tecentriq in 8 (0.3%) patients. Colitis requiring the use of corticosteroids occurred in 0.6% (19/3178) of patients receiving Tecentriq.

Immune-mediated endocrinopathies

Thyroid Disorders

Hypothyroidism occurred in 5.2% (164/3178) of patients who received Tecentriq monotherapy. The median time to onset was 4.9 months (range: 0 to 31.3 months).

Hypothyroidism occurred in 17.4% (86/495) of patients who received Tecentriq monotherapy in the adjuvant NSCLC setting.

Hyperthyroidism occurred in 0.9% (30/3178) of patients who received Tecentriq monotherapy. The median time to onset was 2.1 months (range: 0.7 to 15.7 months). The median duration was 2.6 months (range: 0+ to 17.1+ months; + denotes a censored value).

Hyperthyroidism occurred in 4.9% (23/473) of patients who received Tecentriq in combination with carboplatin and nab-paclitaxel. Hyperthyroidism led to discontinuation in 1 (0.2%) patient.

Hyperthyroidism occurred in 6.5% (32/495) of patients who received Tecentriq monotherapy in the adjuvant NSCLC setting.

Adrenal Insufficiency

Adrenal insufficiency occurred in 0.3% (11/3178) of patients who received Tecentriq monotherapy. The median time to onset was 5.5 months (range: 0.1 to 19.0 months). The median duration was 16.8 months (range: 0 to 16.8 months). Adrenal insufficiency led to discontinuation of Tecentriq in 1 (<0.1%) patient. Adrenal insufficiency requiring the use of corticoteriods occurred in 0.3% (9/3178) of patients receiving Tecentriq.

Adrenal insufficiency occurred in 1.5% (7/473) of patients who received Tecentriq in combination with carboplatin and nab-paclitaxel. Adrenal insufficiency requiring the use of corticosteroids occurred in 0.8% (4/473) of patients receiving Tecentriq in combination with carboplatin and nab-paclitaxel.

Adrenal insufficiency occurred in 1.2% (6/495) of patients who received Tecentriq in the adjuvant NSCLC setting.

Hypophysitis

Hypophysitis occurred in <0.1% (2/3178) of patients who received Tecentriq monotherapy. The median time to onset was 7.2 months (range: 0.8 to 13.7 months). One patient required the use of corticosteroids and treatment with Tecentriq was discontinued.

Hypophysitis occurred in 0.8% (3/393) of patients who received Tecentriq with Avastin, paclitaxel, and carboplatin. The median time to onset was 7.7 months (range: 5.0 to 8.8 months). Two patients required the use of corticosteroids. Hypophysitis lead to the discontinuation of treatment in one patient.

Diabetes Mellitus

Diabetes mellitus occurred in 0.3% (10/3178) of patients who received Tecentriq monotherapy. The median time to onset was 4.2 months (range 0.1 to 9.9 months). The median duration was 1.6 months (range: 0.1 to 15.2+ months; + denotes a censored value). Diabetes mellitus led to the discontinuation of Tecentriq in 3 (<0.1%) patients.

Immune-mediated meningoencephalitis

Meningoencephalitis occurred in 0.4% (14/3178) of patients who received Tecentriq monotherapy. The median time to onset was 0.5 months (range 0 to 12.5 months). The median duration was 0.7 months (range 0.2 to 14.5+ months; + denotes a censored value). Meningoencephalitis requiring the use of corticosteroids occurred in 0.2% (6/3178) of patients receiving Tecentriq and led to discontinuation of Tecentriq in 4 (0.1%) patients.

Immune-mediated neuropathies

Guillain-Barré syndrome and demyelinating polyneuropathy

Guillain-Barré syndrome and demyelinating polyneuropathy, occurred in 0.2% (5/3178) of patients who received Tecentriq monotherapy. The median time to onset was 7.0 months (range: 0.6 to 8.1 months). The median duration was 8.0 months (0.6 to 8.3+ months; + denotes a censored value). Guillain-Barré syndrome led to the discontinuation of Tecentriq in 1 (<0.1%) patient. Guillain-Barré syndrome requiring the use of corticosteroids occurred in <0.1% (2/3178) of patients receiving Tecentriq.

Immune-mediated facial paresis

Facial Paresis occurred in <0.1% (1/3178) of patients who received Tecentriq monotherapy. The time to onset was 29 days. The duration was 1.1 months. The event did not require the use of corticosteroids and the event did not lead to discontinuation of Tecentriq.

Immune-mediated myelitis

Myelitis occurred in <0.1% (1/3178) of patients who received Tecentriq monotherapy. The time to onset was 23 days. The event required the use of corticosteroids but did not lead to discontinuation of Tecentriq.

Immune-mediated pancreatitis

Pancreatitis, including amylase increased and lipase increased, occurred in 0.6% (18/3178) of patients who received Tecentriq monotherapy. The median time to onset was 5.0 months (range: 0.3 to 16.9 months). The median duration was 0.8 months (range 0.1 to 12.0+ months; + denotes a censored value). Pancreatitis led to discontinuation of Tecentriq in 3 (<0.1%) patients. Pancreatitis requiring the use of corticosteroids occurred in <0.1% (4/3178) of patients receiving Tecentriq.

Immune-mediated myositis

Myositis occurred in 0.4% (13/3178) of patients who received Tecentriq monotherapy. The median time to onset was 5.1 months (range: 0.7 to 11.0 months). The median duration was 5.0 months (range 0.7 to 22.6+ months, + denotes a censored value). Myositis led to discontinuation of Tecentriq in 1 (<0.1%) patient. Myositis requiring the use of corticosteroids occurred in 0.2% (7/3178) of patients receiving Tecentriq.

Immune-mediated nephritis

Nephritis, occurred in <0.1% (3/3178) of patients who received Tecentriq monotherapy. The median time to onset was 13.1 months (range: 9.0 to 17.5 months). The median duration was 2.8 months (range 0.5 to 9.5+ months; + denotes a censored value). Nephritis led to discontinuation of Tecentriq in 2 (<0.1%) patients. One patient required the use of corticosteroids.

Immune-mediated severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) occurred in 0.7% (22/3178) of patients who received Tecentriq monotherapy. The median time to onset was 5.9 months (range 0.1 to 15.5 months). The median duration was 1.6 months (range 0 to 22.1+ months; + denotes a censored value). SCARs led to discontinuation of Tecentriq in 3 (<0.1%) patients. SCARs requiring the use of systemic corticosteroids occurred in 0.2% (6/3178) of patients receiving Tecentriq monotherapy.

Immune-mediated pericardial disorders

Pericardial disorders occurred in 1.4% (45/3178) of patients who received Tecentriq monotherapy. The median time to onset was 1.4 months (range 0.2 to 17.5 months). The median duration was 1.4 months (range 0 to 19.3 months). Pericardial disorders led to discontinuation of Tecentriq in 3 (<0.1%) patients. Pericardial disorders requiring the use of corticosteroids occurred in 0.2% (7/3178) patients.

Switching treatment from Tecentriq IV to Tecentriq SC (or vice versa)

Switching from Tecentriq IV to Tecentriq SC (or vice versa) was consistent with the safety profile observed in previous studies using Tecentriq IV administration (see section 3.1.2 Clinical / Efficacy Studies).

2.6.2 Postmarketing Experience

The following adverse reactions have been identified from post marketing surveillance with Tecentriq (see Table 6). Because reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with atezolizumab:
pancreatic exocrine insufficiency

Adverse drug reactions from post marketing surveillance are listed by MedDRA system organ class.

Table 6 Adverse Drug Reactions from Postmarketing Surveillance

System Organ Class **ADR (preferred term, MedDRA)**	**Frequency**
Blood and Lymphatic System Disorders	
Haemophagocytic lymphohistiocytosis[a]	Rare
Cardiac Disorders	
Pericardial disorders[a,b]	Common
Musculoskeletal and connective tissue disorders	
Arthritis (including immune-mediated arthritis)	Unknown
Sjögrens syndrome	Unknown
Tenosynovitis	Unknown
Neoplasms benign, malignant and unspecified	
Sarcoidosis	Unknown
Nervous System Disorders	Rare
Facial paresis[a]	Rare
Myelitis[a]	
Renal and Urinary Disorder	
Renal failure	Unknown

[a]Reported from postmarketing experience outside the pooled dataset. The frequency is based on the program-wide exposure.
[b]Includes reports of pericarditis, pericardial effusion, cardiac tamponade and pericarditis constrictive

2.7 OVERDOSE

There is no information on overdose with Tecentriq.

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No formal pharmacokinetic drug-drug interaction studies have been conducted with atezolizumab. Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 Mechanism of Action

Atezolizumab is produced by recombinant DNA technology.

Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells suppresses cytotoxic T-cell activity through the inhibition of T-cell proliferation and cytokine production. PD-L1 may be expressed on tumor cells and tumor-infiltrating immune cells, and can contribute to the inhibition of the antitumor immune response in the microenvironment.

Atezolizumab is an Fc-engineered humanized immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 pathway-mediated inhibition of the immune response, including reactivating the antitumor immune response. Atezolizumab leaves the PD-L2/PD-1 interaction intact. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

3.1.2 Clinical / Efficacy Studies

Tecentriq SC was only studied in 2L NSCLC patients in IMscin001.

NSCLC

Early-stage NSCLC

IMpower010

A phase III, open label, multi-centre, randomised study, GO29527 (IMpower010), was conducted to evaluate the efficacy and safety of atezolizumab for the adjuvant treatment of patients with stage IB (tumours ≥ 4 cm) – IIIA NSCLC (per the Union for International Cancer Control/American Joint Committee on Cancer staging system, 7th edition). A total of 1,280 enrolled patients had complete tumour resection and were eligible to receive up to 4 cycles of cisplatin-based chemotherapy. The cisplatin-based chemotherapy regimens are described in Table 7.

Table 7 Adjuvant chemotherapy intravenous regimens (IMpower010)

Adjuvant cisplatin-based chemotherapy: Cisplatin 75 mg/m^2 IV on Day 1 of each 21 day cycle with one of the following treatment regimens	Vinorelbine 30 mg/m^2 IV, Day 1 and 8
	Docetaxel 75 mg/m^2 IV, Day 1
	Gemcitabine 1250 mg/m^2 IV, Day 1 and 8
	Pemetrexed 500 mg/m^2 IV, Day 1

After completion of cisplatin-based chemotherapy (up to four cycles), a total of 1005 patients were randomised in a 1:1 ratio to receive atezolizumab (Arm A) or best supportive care (BSC) (Arm B). Atezolizumab was administered as a fixed dose of 1200 mg by IV infusion every 3 weeks for 16 cycles unless there was disease recurrence or unacceptable toxicity. Randomisation was stratified by sex, stage of disease, histology, and PD-L1 expression.

Patients were excluded if they had a history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomisation; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomisation. Tumour assessments were conducted at baseline of the randomisation phase and every 4 months for the first year following Cycle 1, Day 1 and then every 6 months until year five, then annually thereafter.

The demographics and baseline disease characteristics in the ITT population were well balanced between the treatment arms. The median age was 62 years (range: 26 to 84), and 67% of patients were male. The majority of patients were White (73%), and 24% were Asian. Most patients were current or previous smokers (78%) and baseline ECOG performance status in patients was 0 (55%) or 1 (44%). Overall, 12% of patients had stage IB, 47% had stage II and 41% had stage IIIA disease. As measured by the VENTANA PD-L1 (SP263) Assay, 55% of patients had tumors with PD-L1 expression ≥ 1% on TC and 26% of patients had tumors with PD-L1 expression ≥ 50 % on TC.

The primary efficacy outcome measure was disease-free survival (DFS) as assessed by the investigator. DFS was defined as the time from the date of randomisation to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC, or death due to any cause, whichever occurred first. The primary efficacy objective was to evaluate DFS in the PD-L1 ≥ 1% TC stage II to IIIA patient population. Key secondary efficacy objectives were to evaluate DFS in the PD-L1 ≥ 50% TC stage II to IIIA patient population and overall survival (OS) in the ITT population.

At the time of the interim DFS analysis, the study met its primary endpoint and demonstrated a statistically significant improvement in DFS in the atezolizumab arm compared to the BSC arm in the PD-L1 ≥ 1% TC stage II - IIIA patient population (n=476). The median follow-up time was approximately 32 months.

In the secondary objective analysis of patients with PD-L1 TC ≥ 50% stage II to IIIA (n = 229), a clinically meaningful improvement in DFS was shown with an unstratified HR of 0.43 (95% CI: 0.27, 0.68). The median DFS was not reached (95% CI: 42.3 months, NE) for patients in the atezolizumab arm and was 35.7 months (95% CI: 29.7, NE) for patients in the best supportive care arm. The OS data were immature at the time of the DFS interim analysis with approximately 16.2% of deaths reported in both arms in the PD-L1 ≥ 50% TC stage II to IIIA patient population. An exploratory analysis of OS suggested a trend in favour of Tecentriq over BSC, with an unstratified HR of 0.37 (95% CI: 0.18, 0.74) in this patient population.

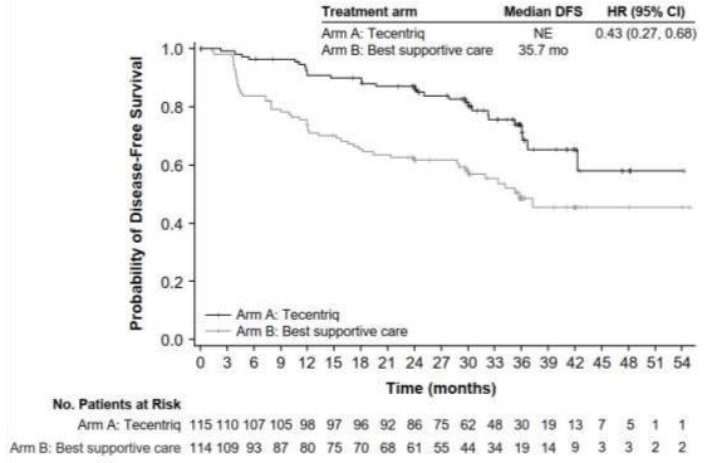
The key efficacy results for the PD-L1 ≥ 50% TC stage II – IIIA patient population are summarised in Table 8. The Kaplan-Meier curve for DFS is presented in Figure 1.

Table 8 Summary of efficacy for the PD-L1 expression ≥ 50% TC stage II - IIIA patient population (IMpower010)

Efficacy endpoint	**Arm A** (Atezolizumab)	**Arm B** (Best supportive care)
Investigator-assessed DFS	n = 115	n = 114
No. of events (%)	28 (24.3%)	52 (45.6%)
Median duration of DFS (months)	NE	35.7
95% CI	42.3, NE	29.7, NE
Unstratified hazard ratio* (95% CI)	0.43 (0.27, 0.68)	
3-year DFS rate (%)	73.8	48.6

DFS = Disease-free survival; CI = confidence interval; NE = not estimable

Figure 1 Kaplan-Meier curve for disease-free survival in the PD-L1 expression >=50%TC stage II - IIIA patient population (IMpower010)



The observed DFS improvement in the atezolizumab arm compared with the BSC arm was consistently shown across the majority of pre-specified subgroups in the PD-L1 ≥ 50% TC stage II - IIIA patient population including both non-squamous NSCLC patients (unstratified HR: 0.36 [95% CI: 0.20, 0.65], median DFS NE vs. 34.2 months) and squamous NSCLC patients (unstratified HR: 0.60 [95% CI: 0.29, 1.26], median DFS 36.7 vs. NE months).

1L metastatic non-squamous NSCLC

IMpower150

A phase III, open-label, randomized study, GO29436 (IMpower150), was conducted to evaluate the efficacy and safety of Tecentriq in combination with paclitaxel and carboplatin, with or without Avastin, in chemotherapy-naïve patients with metastatic non-squamous NSCLC. A total of 1202 patients were enrolled and were randomized in a 1:1:1 ratio to receive one of the treatment regimens described in Table 9. Randomization was stratified by sex, presence of liver metastases and PD-L1 tumor expression on tumor cells (TC) and tumor infiltrating cells (IC).

Table 9 Intravenous Treatment regimens in Study IMpower150

Treatment regimen	**Induction (Four or Six 21-day cycles)**	**Maintenance (21-day cycles)**
A	Tecentriq[a] (1200 mg) + paclitaxel[b,c] (200 mg/m^2) + carboplatin[c] (AUC 6)	Tecentriq[a] (1200 mg)
B	Tecentriq[a] (1200 mg) + Avastin[d] (15 mg/kg) + paclitaxel[b,c] (200 mg/m^2) + carboplatin[c] (AUC 6)	Tecentriq[a] (1200 mg) + Avastin[d] (15 mg/kg)
C	Avastin[d] (15 mg/kg) + paclitaxel[b,c] (200 mg/m^2) + carboplatin[c] (AUC 6)	Avastin[d] (15 mg/kg)

[a]Tecentriq is administered until loss of clinical benefit as assessed by the investigator
[b]The paclitaxel starting dose for patients of Asian race/ethnicity was 175 mg/m^2 due to higher overall level of hematologic toxicities in patients from Asian countries compared with those from non-Asian countries.
[c]Carboplatin and paclitaxel are administered until completion of 4 or 6 cycles, or progressive disease or unacceptable toxicity whichever occurs first
[d]Avastin is administered until progressive disease or unacceptable toxicity

Patients were excluded if they had history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; active or untreated CNS metastases; clear tumor infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging. Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter.

The demographics and baseline disease characteristics of the study population were well balanced between the treatment arms. In this study, the median age was 63 years (range: 31 to 90), and 60% of patients were male. The majority of patients were white (82%). Approximately 10% of patients had known EGFR mutations, 4% had known ALK rearrangements, 14% had liver metastases at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%).

At the time of the final analysis for PFS, patients had a median follow up time of 15.3 months. The ITT population, including patients with EGFR mutations or ALK rearrangements who should have been previously treated with tyrosine kinase inhibitors, demonstrated PFS improvement in Arm B as compared to Arm C (HR: 0.61 [95% CI: 0.52, 0.72] median PFS 8.3 vs. 6.8 months.

At the time of the interim OS analysis, patients had a median follow up time of 19.7 months. Key results from this analysis are summarized in Table 10. Kaplan-Meier curves for OS in the ITT population are presented in Figure 2. Figure 3 summarizes the results of OS in the ITT and PD-L1 subgroups, demonstrating OS benefit with Tecentriq in all subgroups, including those with PD-L1 expression <1% on TC and IC. Updated PFS results are also demonstrated in Figures 4 and 5.

Table 10 Summary of updated efficacy from IMpower150

Key efficacy endpoints	Arm B	Arm C
OS interim analysis	n=400	n=400
No. of deaths (%)	192 (48.0%)	230 (57.5%)
Median time to events (months)	19.8	14.9
95% CI	(17.4, 24.2)	(13.4, 17.1)
Stratified hazard ratio (95% CI)	0.76 (0.63, 0.93)	
p-value [1,2]	0.006	
6-month OS (%)	85	81
12-month OS (%)	68	61
Investigator-assessed PFS (RECIST v1.1)	n=400	n=400
No. of events (%)	291(72.8%)	355 (88.8%)
Median duration of PFS (months)	8.4	6.8
95% CI	(8.0, 9.9)	(6.0, 7.0)
Stratified hazard ratio‡ (95% CI)	0.59 (0.50, 0.69)	
p-value [1,2]	< 0.0001	
12-month PFS (%)	38	20
Investigator-assessed Overall Best Response[3] (RECIST 1.1)	n=397	n=393
No. of responders (%)	224 (56.4%)	158 (40.2%)
95% CI	(51.4, 61.4)	(35.3, 45.2)
No. of complete response (%)	11 (2.8%)	3 (0.8%)
No. of partial response (%)	213 (53.7%)	155 (39.4%)
Investigator-assessed DOR (RECIST 1.1)	n=224	n=158
Median in months	11.5	6.0
95% CI	(8.9, 15.7)	(5.5, 6.9)

1. Based on the stratified log-rank test
2. For informational purposes; comparisons between Arm B and Arm C in the ITT population were not formally tested yet, as per the pre-specified analysis hierarchy.
3. Overall best response for complete response and partial response

‡ Stratified by sex, presence of liver metastases and PD-L1 tumor expression on TC and IC

PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1.; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival

Figure 2: Kaplan-Meier Plot for Overall Survival in the ITT population (IMpower150)

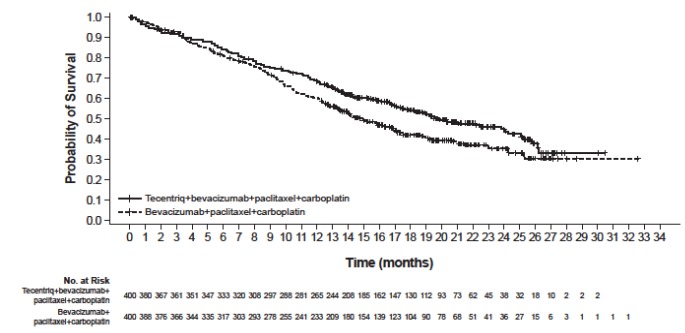


Figure 3: Forest plot of overall survival by PD-L1 expression in the ITT population (IMpower150)

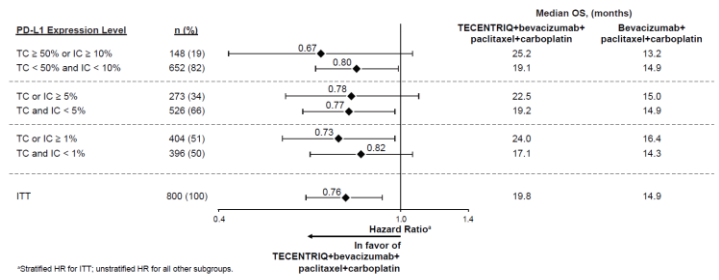


Figure 4: Kaplan-Meier Plot for updated Progression Free Survival in the ITT population (IMpower150)

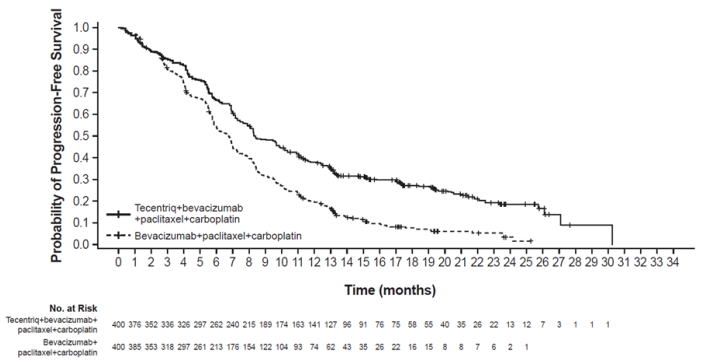
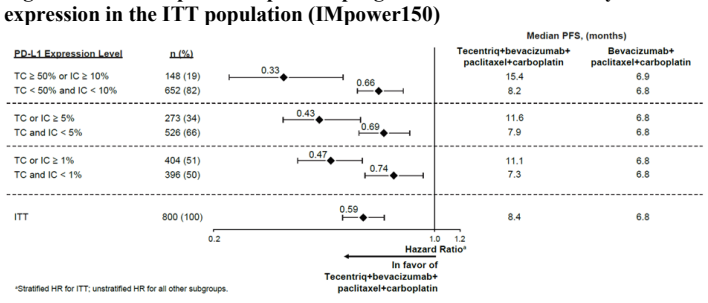


Figure 5: Forest plot of updated progression free survival by PD-L1 expression in the ITT population (IMpower150)



Pre-specified subgroup analyses from the interim OS analysis showed a numerical OS improvements in the Tecentriq with Avastin, paclitaxel, carboplatin arm as compared to the Avastin, paclitaxel and carboplatin arm for patients with EGFR mutations or ALK rearrangements (HR: 0.54 [95% CI: 0.29, 1.03], median OS NE vs. 17.5 months) and liver metastases (HR: 0.52 [95% CI: 0.33, 0.82], median OS 13.3 vs 9.4 months). Numerical PFS improvements were also shown in patients with EGFR mutations or ALK rearrangements (HR: 0.55 [95% CI 0.34, 0.90], median PFS 10 vs. 6.1 months) and liver metastases (HR: 0.41 [95%CI 0.26, 0.62], median PFS 8.2 vs. 5.4 months).

This study also evaluated Physical Function and Patient-Reported Treatment-Related Symptoms using the EORTC QLQ-C30 and EORTC QLQ-LC13 measures at the time of the final PFS analysis. On average, patients who received Tecentriq with Avastin, paclitaxel and carboplatin reported minimal treatment burden as indicated by minimal deterioration in both Physical Function and Patient-Reported Treatment-Related Symptom Scores (i.e. fatigue, constipation, diarrhea, nausea/vomiting, hemoptysis, dysphagia, and sore mouth) while on treatment. Average patient-reported physical function and treatment-related symptom scores in both patients who received Tecentriq with Avastin, paclitaxel and carboplatin as well as patients who received Avastin in combination with paclitaxel and carboplatin, were comparable while on treatment.

IMpower130

A Phase III, open-label, randomized study, GO29537 (IMpower130) was conducted to evaluate the efficacy and safety of Tecentriq in combination with nab-paclitaxel and carboplatin, in chemotherapy-naïve patients with metastatic non-squamous NSCLC. Patients including those with EGFR or ALK genomic tumor aberrations, were enrolled and were randomized in a 2:1 ratio to receive one of the treatment regimens described in Table 11. Randomization was stratified by sex, presence of liver metastases and PD-L1 tumor expression on tumor cells (TC) and tumor infiltrating cells (IC). Patients in treatment regimen B were able to crossover and receive Tecentriq monotherapy following disease progression.

Table 11 Intravenous treatment regimens in IMpower130

Treatment Regimen	Induction (Four or Six 21-Day Cycles)	Maintenance (21-Day Cycles)
A	Tecentriq (1200mg)[a] + nab-paclitaxel (100mg/m^2)[b,c] + carboplatin (AUC 6)[c]	Tecentriq (1200mg) [a]
B	Nab-paclitaxel (100mg/m^2)[b] + Carboplatin (AUC 6)[c]	Best supportive care or pemetrexed

[a] Tecentriq is administered until loss of clinical benefit as assessed by investigator
[b] Nab-paclitaxel is administered on days 1, 8, and 15 of each cycle
[c] Nab-paclitaxel and carboplatin and is administered until completion of 4-6 cycles, or progressive disease or unacceptable toxicity whichever occurs first

Patients were excluded if they had history of autoimmune disease, administration of live, attenuated vaccine within 28 days prior to randomization, administration of immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization, and active or untreated CNS metastases. Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, then every 9 weeks thereafter.

The demographics and baseline disease characteristics of the study population (n = 723) were well balanced between the treatment arms. The median age was 64 years (range 18 to 86). The majority of the patients were, male (57%), white (90%). 14.8% of patients had liver metastases at baseline, and most patients were current or previous smokers (88%). The majority of patients had baseline ECOG performance status of 1 (58.7%).

The primary analysis was conducted in all patients, excluding those with EGFR or ALK genomic tumor aberrations (n = 679). Patients had a median survival follow up time of 18.6 months. Improvements in OS and PFS were demonstrated with Tecentriq + nab-paclitaxel + carboplatin compared to the control. The key results are summarized in Table 12 and Kaplan-Meier curves for OS and PFS are presented in Figures 6 and 8, respectively.

All PD-L1 subgroups, regardless of expression, derived benefit in terms of OS and PFS; the results are summarized in Figure 7 and 9. Consistent OS and PFS benefit was demonstrated in all other pre-specified subgroups, with the exception of patients with liver metastases who did not show improved OS with Tecentriq, nab-paclitaxel and carboplatin, compared to nab-paclitaxel and carboplatin (HR of 1.04, 95% CI: 0.63,1.72).

Approximately 66% of patients in the nab-paclitaxel and carboplatin arm received any anti-cancer therapy after disease progression compared to 39% in the Tecentriq, nab-paclitaxel and carboplatin arm. These included, approximately 59% of patients in the nab-paclitaxel and carboplatin arm received any cancer immunotherapy after disease progression, which includes Tecentriq as crossover (41% of all patients), compared to 7.3% in the Tecentriq, nab-paclitaxel and carboplatin arm.

Table 12 Summary of efficacy from IMpower130 in the Primary Analysis Population

Key efficacy endpoints	Tecentriq + nab-paclitaxel + carboplatin	nab-paclitaxel + carboplatin
Co-primary Endpoints		
OS	n = 451	n = 228
No. of deaths (%)	226 (50.1%)	131 (57.5%)
Median time to events (months)	18.6	13.9
95% CI	(16.0, 21.2)	(12.0, 18.7)
Stratified hazard ratio‡ (95% CI)	0.79 (0.64, 0.98)	
p-value	0.033	
12-month OS (%)	63	56
Investigator-assessed PFS (RECIST v1.1)	n = 451	n = 228
No. of events (%)	347 (76.9)	198 (86.8)
Median duration of PFS (months)	7.0	5.5
95% CI	(6.2, 7.3)	(4.4, 5.9)
Stratified hazard ratio‡ (95% CI)	0.64 (0.54, 0.77)	
p-value	< 0.0001	
12-month PFS (%)	29	14
Secondary Endpoints		
Investigator-assessed ORR (RECIST 1.1)	n = 447	n = 226
No. of confirmed responders (%)	220 (49.2%)	72 (31.9%)
95% CI	(44.5, 54.0)	(25.8, 38.4)
No. of complete response (%)	11 (2.5%)	3 (1.3%)
No. of partial response (%)	209 (46.8%)	69 (30.5%)
Investigator-assessed confirmed DOR (RECIST 1.1)	n = 220	n = 72
Median in months	8.4	6.1
95% CI	(6.9, 11.8)	(5.5, 7.9)

‡ Stratified by sex and PD-L1 tumor expression on TC and IC
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1.; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival

Figure 6: Kaplan-Meier Plot for Overall Survival (IMpower130)

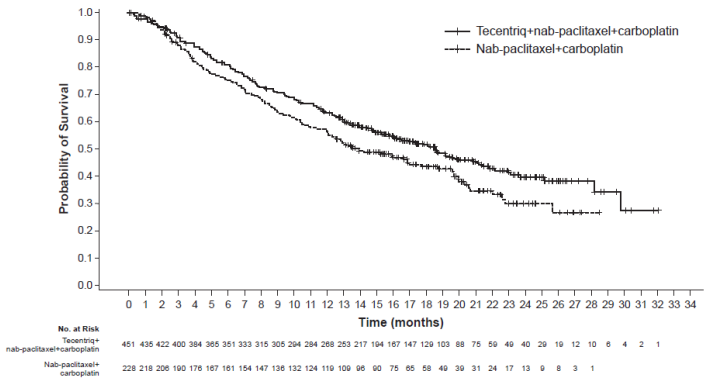


Figure 7: Forest Plot of Overall Survival by PD-L1 expression (IMpower130)

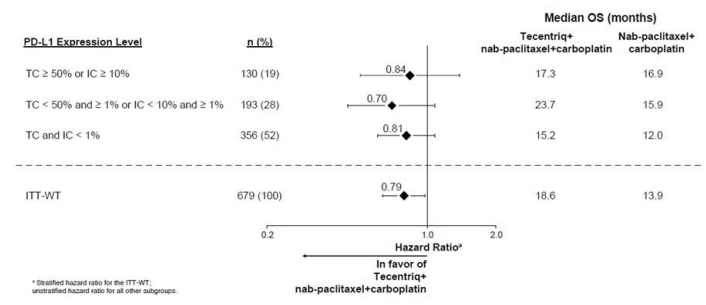


Figure 8: Kaplan-Meier Plot for Progression Free Survival (IMpower130)

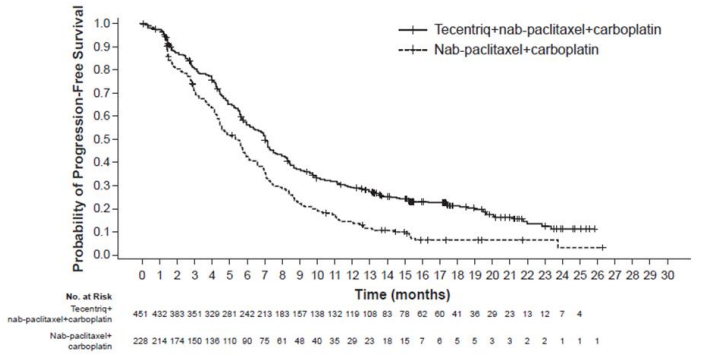
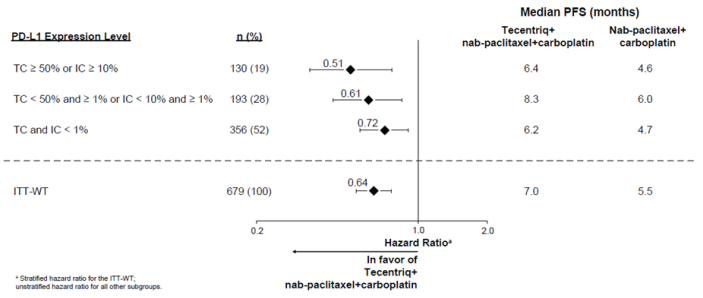


Figure 9: Forest Plot of Progression Free Survival by PD-L1 expression (IMpower130)



The study also evaluated Physical Function and Patient Reported Treatment-Related Symptoms using the EORTC QLQ-C30 and EORTC QLQ-LC13 measures. On average, patients who received Tecentriq with nab-paclitaxel and carboplatin reported high functioning and no clinically meaningful worsening in treatment-related symptoms. There was no difference in delay of lung-related symptoms (dyspnea, cough and chest pain) however patients receiving Tecentriq, nab-paclitaxel and carboplatin reported less worsening of these symptoms over time.

1L metastatic non-squamous and squamous NSCLC
IMpower110

A phase III, open-label, multi-center, randomized study, GO29431 (IMpower110), was conducted to evaluate the efficacy and safety of Tecentriq in chemotherapy-naïve patients with metastatic NSCLC, with PD-L1 expression ≥ 1% TC (PD-L1 stained ≥ 1% of tumor cells) or ≥ 1% IC (PD-L1 stained tumor-infiltrating immune cells covering ≥ 1% of the tumor area) by the VENTANA PD-L1 (SP142) Assay.

A total of 572 patients were randomized in a 1:1 ratio to receive Tecentriq (Arm A) or chemotherapy (Arm B). Tecentriq was administered as a fixed dose of 1200 mg by IV infusion every 3 weeks until loss of clinical benefit as assessed by the investigator or unacceptable toxicity. The chemotherapy regimens are described in Table 13. Randomization was stratified by sex, ECOG performance status, histology, and PD-L1 tumor expression on TC and IC.

Table 13 Chemotherapy Intravenous Treatment Regimens in Study IMpower110

Treatment regimen	Induction (Four or Six 21-day cycles)	Maintenance (21-day cycles)
B (Non-squamous)	Cisplatin[a] (75 mg/m²) + pemetrexed[a] (500 mg/m²) OR carboplatin[a] (AUC 6) + pemetrexed[b] (500 mg/m²)	Pemetrexed[b, d] (500 mg/m²)
B (Squamous)	Cisplatin[a] (75 mg/m²) + gemcitabine[a,c] (1250 mg/m²) OR carboplatin[a] (AUC 5) + gemcitabine[a,c] (1000 mg/m²)	Best supportive care[d]

[a] Cisplatin, carboplatin, pemetrexed and gemcitabine are administered until completion of 4 or 6 cycles, or progressive disease or unacceptable toxicity
[b] Pemetrexed is administered as maintenance regimen every 21 days until progressive disease or unacceptable toxicity
[c] Gemcitabine is administered on days 1 and 8 of each cycle
[d] No crossover was allowed from the control arm (platinum-based chemotherapy) to the Tecentriq arm (Arm A)

Patients were excluded if they had history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; active or untreated CNS metastases. Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter.

The demographics and baseline disease characteristics in patients with PD-L1 expression ≥ 1% TC or ≥ 1% IC who do not have EGFR or ALK genomic tumor aberrations (n=554) were well balanced between the treatment arms. The median age was 64.5 years (range: 30 to 87), and 70% of patients were male. The majority of patients were white (84%) and Asian (14%). Most patients were current or previous smokers (87%) and baseline ECOG performance status in patients was 0 (36%) or 1 (64%). Overall, 69% of patients had non-squamous disease and 31% of patients had squamous disease. The demographics and baseline disease characteristics in patients with high PD-L1 expression (PD-L1 ≥ 50% TC or ≥ 10% IC) who do not have EGFR or ALK genomic tumor aberrations (n=205) were generally representative of the broader study population and were balanced between the treatment arms.

The primary endpoint was overall survival (OS). At the time of the interim OS analysis, patients with high PD-L1 expression excluding those with EGFR or ALK genomic tumor aberrations (n=205) demonstrated statistically significant improvement in OS for the patients randomized to Tecentriq (Arm A) as compared with chemotherapy (Arm B). The median survival follow-up time in patients with high PD-L1 expression was 15.7 months. The key results are summarized in Table 14. The Kaplan-Meier curves for OS and PFS in patients with high PD-L1 expression are presented in Figure 10 and 11.

Table 14 Summary of efficacy from IMpower110 in patients with high PD-L1 expression (≥ 50% TC or ≥ 10% IC by the VENTANA PD-L1 [SP142] Assay)

Key efficacy endpoints	Arm A (Tecentriq)	Arm B (Chemotherapy)
Primary endpoint		
OS analysis	n=107	n=98
No. of deaths (%)	44 (41.1%)	57 (58.2%)
Median time to events (months)	20.2	13.1
95% CI	(16.5, NE)	(7.4, 16.5)
Stratified hazard ratio‡ (95% CI)	0.59 (0.40, 0.89)	
p-value‡	0.0106	
12-month OS (%)	64.9	50.6
Secondary endpoints		
Investigator-assessed PFS (RECIST v1.1)	n=107	n=98
No. of events (%)	67 (62.6%)	79 (80.6%)
Median duration of PFS (months)	8.1	5.0
95% CI	(6.8, 11.0)	(4.2, 5.7)
Stratified hazard ratio‡ (95% CI)	0.63 (0.45, 0.88)	
12-month PFS (%)	36.9	21.6
Investigator-assessed ORR (RECIST 1.1)	n = 107	n = 98
No. of responders (%)	41 (38.3%)	28 (28.6%)
95% CI	(29.1, 48.2)	(19.9, 38.6)
No. of complete response (%)	1 (0.9%)	1 (1.0%)
No. of partial response (%)	40 (37.4%)	27 (27.6%)
Investigator-assessed DOR (RECIST 1.1)	n = 41	n = 28
Median in months	NE	6.7
95% CI	(11.8, NE)	(5.5, 17.3)

‡ Stratified by sex and ECOG performance status (0 vs 1). Interim analysis for OS was tested at a two-sided α of 0.0413 for the TC3 or IC3 population
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival; NE=not estimable.

Figure 10: Kaplan-Meier Plot of Overall Survival in Patients with high PD-L1 Expression (≥ 50% TC or ≥ 10% IC)

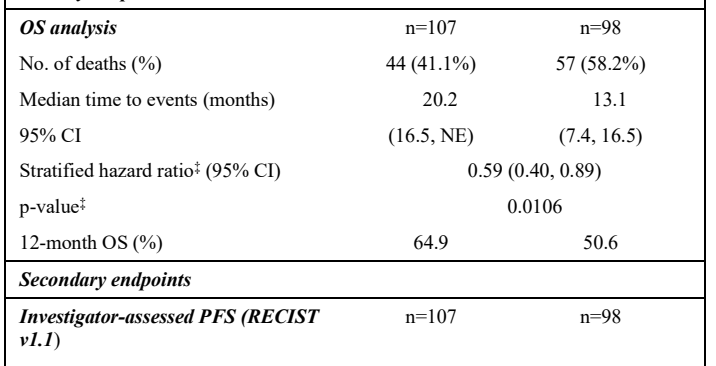
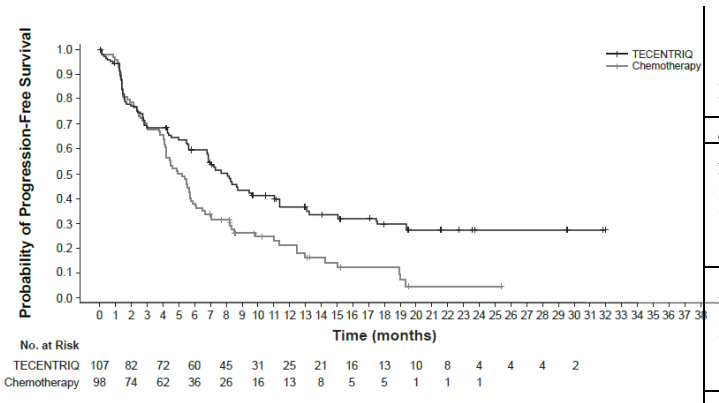


Figure 11: Kaplan-Meier Plot of Progression Free Survival in Patients with high PD-L1 Expression (≥ 50% TC or ≥ 10% IC)



The observed OS improvement in the Tecentriq arm compared with the chemotherapy arm was consistently demonstrated across subgroups in patients with high PD-L1 expression including both non-squamous NSCLC patients (HR: 0.62 [95% CI: 0.40, 0.96], median OS 20.2 vs. 10.5 months) and squamous NSCLC patients (HR: 0.56 [95% CI: 0.23, 1.37]) median OS NE vs 15.3 months). The data for patients ≥75 years old (HR: 1.04 [95% CI: 0.19, 5.70] in those aged 75 to 84 years) and patients who were never smokers (HR: 1.83 [95% CI: 0.63, 5.31]) are too limited to draw conclusions due to the small numbers of patients (n=22 and 24, respectively) in these subgroups.

Additional pre-specified analyses were conducted to evaluate efficacy by PD-L1 status assessed by the VENTANA PD-L1 (SP263) Assay and by the PD-L1 IHC 22C3 pharmDxTM kit in all randomized patients with PD-L1 expression ≥ 1% TC or ≥ 1% IC by the VENTANA PD-L1 (SP142) Assay who do not have EGFR or ALK genomic tumour abberations (n=554). An OS improvement was observed with atezolizumab compared to chemotherapy in patients with high PD-L1 expression (PD-L1 ≥50% TC) using the VENTANA PD-L1 (SP263) Assay (n=293; HR: 0.71 [95% CI: 0.50, 1.00], median OS 19.5 vs. 16.1 months) and in patients with high PD-L1 expression (Tumour Proportion Score (TPS) ≥50%) using the PD-L1 IHC 22C3 pharmDxTM Kit (n=260; HR: 0.60 [95% CI: 0.42, 0.86], median OS 20.2 vs 11.0 months).

The study also evaluated Patient Reported Physical Function, Global Health Status/Health Related Quality of Life and Lung Related Symptoms using the EORTC QLQ-C30, EORTC QLQ-LC13, and SILC measures at the time of interim OS analysis. Time to deterioration of lung-related symptoms (dyspnea, cough, and chest pain) as measured by the SILC and EORTC QLQ-LC13 was similar in both treatment groups indicating that patients maintained low disease burden for a comparable duration of time. These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

1L locally advanced, unresectable, or metastatic NSCLC who are ineligible for platinum-based chemotherapy

MO29872 (IPSOS)
A phase III, open label, randomized, controlled study, MO29872 (IPSOS), was conducted to evaluate the efficacy and safety of Tecentriq compared with a single-agent chemotherapy regimen (vinorelbine or gemcitabine by investigator choice) in treatment- naïve patients with advanced or recurrent (Stage IIIB if not amenable to multimodality treatment) or metastatic (Stage IV) NSCLC as per the American Joint Committee on Cancer (AJCC) 7th edition, who were considered ineligible for any platinum-based chemotherapy either due to poor performance status (ECOG PS of 2 or 3) or, for patients with an ECOG PS of 0 or 1, due to older age (≥70) in combination with substantial comorbidities or other contraindications to platinum-based treatment. Patients with treated asymptomatic CNS metastases were permitted. Patients were eligible regardless of their tumor PD-L1 status.

A total of 453 patients were enrolled in the study (ITT population) and randomized in a 2:1 ratio to receive Tecentriq (Arm A) or chemotherapy (Arm B). Tecentriq was administered as a fixed dose of 1200 mg by intravenous infusion every 3 weeks until disease progression per RECIST v1.1 or unacceptable toxicity. Patients who showed evidence of clinical benefit could continue to receive Tecentriq beyond disease progression until loss of clinical benefit as assessed by the investigator. The chemotherapy regimens are described in Table 15. Randomization was stratified by histology, PD-L1 expression and brain metastases.

Table 15 Treatment Regimens (MO29872)

Treatment Regimen	
A	Tecentriq 1200 mg by IV infusion on Day 1 of every 21-day cycle.
B	Vinorelbine: IV infusion at 25-30 mg/m² or oral administration at 60-80 mg/m² on Days 1 and 8 of each 21-day cycle or on Days 1, 8 and 15 of each 28-day cycle or weekly administration. Gemcitabine: IV infusion at 1000-1250 mg/m² on Days 1 and 8 of each 21-day cycle or on Days 1, 8 and 15 of each 28-day cycle.

The study excluded patients younger than 70 years who had an ECOG PS of 0 or 1; patients with active or untreated CNS metastases; administration of live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory or systemic immunosuppressive medicinal products within 4 weeks prior to randomization. Patients with EGFR mutations or ALK rearrangements were also excluded from the study.

The treatment arms were generally well balanced with respect to demographic and baseline characteristics. The population predominantly comprised White (65.8%) and male (72.4%) patients. The median age of patients was 75 years and 72.8% of patients were aged 70 years or older. The proportion of patients with ECOG PS of 0, 1, 2 and 3 was 1.5%, 15.0%, 75.9%, and 7.5%, respectively. Patients aged ≥ 70 years with an ECOG PS of 0 or 1 comprised 16.6% of the ITT population. Overall, 13.7% of patients had stage IIIB disease not amenable to multimodality treatment and 86.3% had stage IV disease. The percentage of patients who had tumours with PD-L1 expression TC < 1%, 1-49% and ≥ 50% as measured by the VENTANA PD-L1 (SP263) assay was 46.8%, 28.7% and 16.6%, respectively, while 7.9% of patients had an unknown PD-L1 expression status.

The primary endpoint of the study was overall survival (OS). At the time of the final OS analysis, the median follow-up was 41.0 months. Tecentriq demonstrated a statistically significant improvement in OS compared with single-agent chemotherapy (stratified HR: 0.78 [95% CI: 0.63, 0.97; p = 0.028], median OS: 10.3 months vs. 9.2 months) (Table 16 and Figure 12). The secondary endpoint of OS rate at 24 months was 24.3% with Tecentriq compared to 12.4% with chemotherapy.

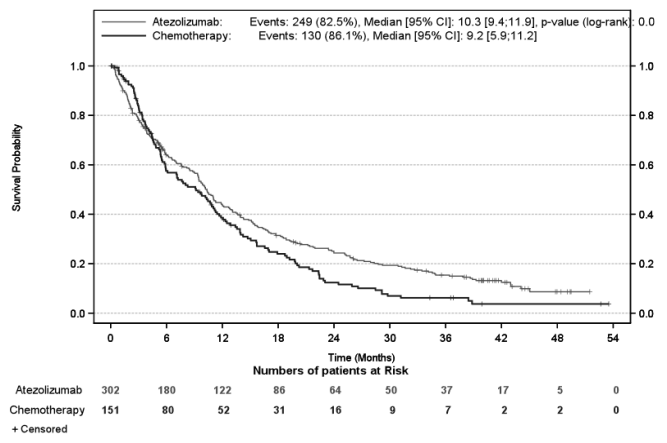
Table 16 Summary of Efficacy (MO29872)

Efficacy endpoint	Tecentriq (N = 302)	Chemotherapy (N = 151)
Primary efficacy endpoint		
OS		
No. of events (%)	249 (82.5%)	130 (86.1%)
Median time to events (months)	10.3	9.2
95% CI	9.4, 11.9	5.9, 11.2
Stratified hazard ratio (95% CI)‡	0.78 (0.63, 0.97)	
p-value (Stratified Log-rank)	p = 0.028	
Secondary endpoints		
Investigator-assessed PFS (RECIST 1.1)		
No. of events (%)	276 (91.4%)	138 (91.4%)
Median duration of PFS (months)	4.2	4.0
95% CI*	3.7, 5.5	2.9, 5.4
Stratified hazard ratio (95% CI)‡	0.87 (0.70, 1.07)	
ORR (RECIST 1.1)		
No. of confirmed responders (%)	51 (16.9%)	12 (7.9%)
Difference in ORR (95% CI)	8.9% (2.4, 15.5)	
No. of complete response (%)	4 (1.3%)	0 (0.0%)
No. of partial response (%)	47 (15.6%)	12 (7.9%)
DOR (RECIST 1.1)		
No (%) of responders	40 (78.4%)	12 (100.0%)
Median in months	14.0	7.8
95% CI*	8.1, 20.3	4.8, 9.7
OS		
6-months OS (%, [95% CI])	64.0 (58.6, 69.5)	57.5 (49.4, 65.7)
12-months OS	43.7 (37.9, 49.4)	38.6 (30.5, 46.7)
18-months OS	31.4 (26.0, 36.8)	24.0 (16.8, 31.2)
24-months OS	24.3 (19.3, 29.4)	12.4 (6.7, 18.0)

CI = confidence interval; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors v1.1.
‡ Estimated hazard ratio and 95% CI obtained from Cox model with treatment group as covariate. For the stratified analysis, histologic subtype, PD-L1 IHC status and brain metastases (yes/no) were added as stratification factors.

A post-hoc exploratory analysis of OS at 30 and 36 months showed numerically higher OS rates for patients in the Tecentriq arm compared with the chemotherapy arm in the ITT population, consistent with the trend observed for other time points. The percentage of patients alive at 30 months was 19.3% (95% CI: 14.6, 24.0) in the Tecentriq arm and 7.0% (95% CI: 2.6, 11.3) in the chemotherapy arm; and at 36 months was 15.4% (95% CI: 11.1, 19.7) in the Tecentriq arm and 6.2% (95% CI: 2.1, 10.3) in the chemotherapy arm.

Figure 12: Kaplan-Meier Plot of Overall Survival (MO29872)



1L ES - SCLC
IMpower133
A Phase I/III, randomized, multicenter, double-blind, placebo controlled study, GO30081 (IMpower133), was conducted to evaluate the efficacy and safety of Tecentriq in combination with carboplatin and etoposide in patients with chemotherapy-naïve ES-SCLC. A total of 403 patients were randomized (1:1) to receive one of the treatment regimens described in Table 17. Randomization was stratified by sex, ECOG performance status, and presence of brain metastases.

This study excluded patients who had active or untreated CNS metastases; history of autoimmune disease; administration of live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunosuppressive medications within 1 week prior to randomization. Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Patients treated beyond disease progression had tumor assessment conducted every 6 weeks until treatment discontinuation.

Table 17 Intravenous Treatment Regimen in Study IMpower133

Treatment regimen	Induction (Four 21-Day Cycles)	Maintenance (21-Day Cycles)
A	Tecentriq (1200 mg)[a] + carboplatin (AUC 5)[b] + etoposide (100 mg/m²)[b,c]	Tecentriq (1200 mg)[a]
B	placebo + carboplatin (AUC 5)[b] + etoposide (100 mg/m²)[b,c]	placebo

[a] Tecentriq is administered until loss of clinical benefit as assessed by investigator
[b] Carboplatin and etoposide is administered until completion of 4 cycles, or progressive disease or unacceptable toxicity whichever occurs first
[c] Etoposide is administered on day 1, 2 and 3 of each cycle

The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 64 years (range: 26 to 90 years). The majority of patients were male (65%), white (80%), and 9% had brain metastases and most patients were current or previous smokers (97%). Baseline ECOG performance status was 0 (35%) or 1 (65%).

At the time of the primary analysis, patients had a median survival follow up time of 13.9 months. The key results are summarized in Table 18. Kaplan-Meier curves for OS and PFS are presented in Figure 13 and 14.

Table 18 Summary of efficacy from IMpower133

Parameter	Interim OS Analysis (CCOD 24 April 2018)		Updated OS Analysis (CCOD 24 January 2019)	
	Arm A (Tecentriq + carboplatin + etoposide)	Arm B (Placebo + carboplatin + etoposide)	Arm A (Tecentriq + carboplatin + etoposide)	Arm B (Placebo + carboplatin + etoposide)
Co-primary endpoints: Overall Survival				
OS analysis	n=201	n=202	n=201	n=202
No. of deaths (%)	104 (51.7%)	134 (66.3%)	142 (70.6)	160 (79.2)
Median time to events (months)	12.3	10.3	12.3	10.3
95% CI	(10.8, 15.9)	(9.3, 11.3)	(10.8, 15.8)	(9.3, 11.3)
Stratified hazard ratio‡ (95% CI)	0.70 (0.54, 0.91)		0.76 (0.60, 0.95)	
p-value	0.0069[a]		0.0154[b]	
12-month OS (%)	51.7	38.2	51.9	39.0
18-month OS (%)	25.0	20.2	34.0	21.0
24-month OS (%)	NE	NE	22.0	16.8
Investigator-assessed PFS (RECIST v1.1)	n=201	n=202		
No. of events (%)	171 (85.1%)	189 (93.6%)		
Median duration of PFS (months)	5.2	4.3		
95% CI	(4.4, 5.6)	(4.2, 4.5)		
Stratified hazard ratio‡ (95% CI)	0.77 (0.62, 0.96)		NA	NA
p-value	0.0170			
6-month PFS (%)	30.9	22.4		
12-month PFS (%)	12.6	5.4		
Secondary endpoints				
Investigator-assessed ORR (RECIST 1.1)	n=201	n=202		
No. of responders (%)	121 (60.2%)	130 (64.4%)		
95% CI	(53.1, 67.0)	(57.3, 71.0.)	NA	NA
No. of complete response (%)	5 (2.5%)	2 (1.0%)		
No. of partial response (%)	116 (57.7%)	128 (63.4%)		
Investigator-assessed DOR (RECIST 1.1)	n =121	n = 130		
Median in months	4.2	3.9	NA	NA
95% CI	(4.1, 4.5)	(3.1, 4.2)		

PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1.; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival; CCOD=Clinical cut-off date; ITT=intent-to-treat; NE=not estimable. NA=No Data

‡ Stratified by sex and ECOG performance status

[a] Interim Analysis OS was tested at two-sided α of 0.0193 (with 238 observed OS events at CCOD) to control the overall two-sided type I error for OS at 0.045 by Lan DeMets function approximating O'Brien-Fleming boundary.

[b] Descriptive purposes only

Figure 13: Kaplan-Meier Curves for Overall Survival (IMpower133) – Updated Analysis (ITT Population)

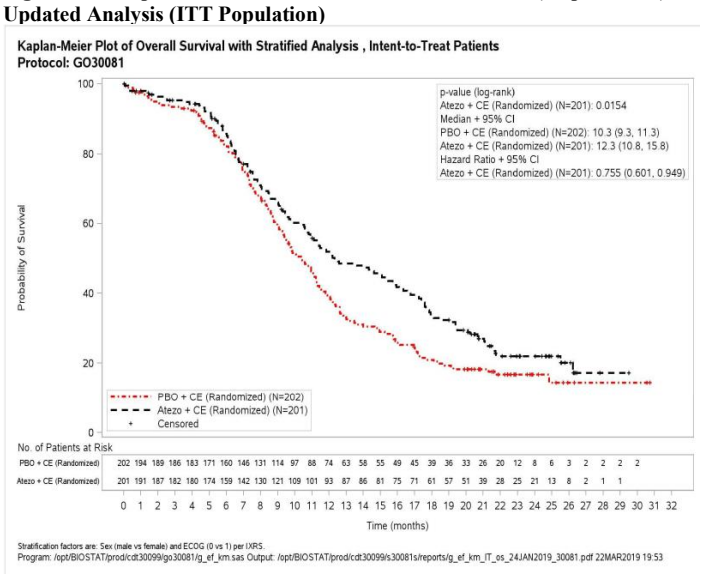
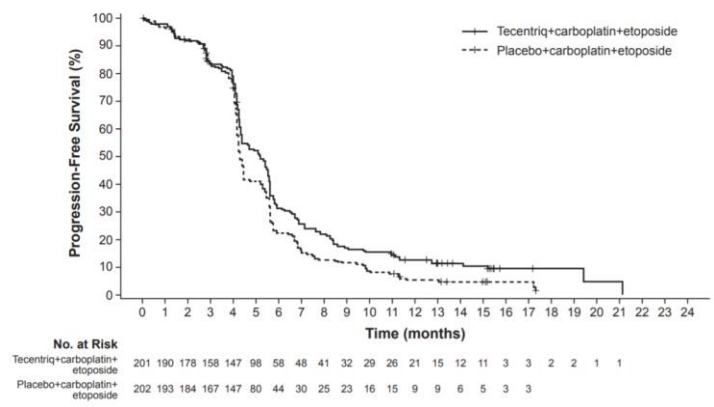


Figure 14: Kaplan-Meier Plot of Progression-Free Survival (IMpower133)



This study also included an exploratory analysis of average score changes from baseline in patient-reported symptoms, physical function, and health-related quality of life (measured using the EORTC QLQ-C30 and QLQ-LC13). On average, patients who received Tecentriq with carboplatin and etoposide reported early and notable improvements in lung cancer-related symptoms (e.g., coughing, chest pain, dyspnea) and physical function. Changes in treatment-related symptoms (e.g., diarrhea, nausea and vomiting, sore mouth, peripheral neuropathy) were comparable between arms throughout induction and most visits through week 54. Overall, patients treated with Tecentriq, carboplatin and etoposide achieved more pronounced and enduring improvements in health-related quality of life (≥10-point score increases at most visits through Week 48) compared to patients treated with placebo, carboplatin and etoposide, who reported nominal improvements (<10-point score increases) at most study treatment visits.

2L NSCLC

Tecentriq IV

OAK

A phase III, open-label, multi-center, international, randomized study, GO28915 (OAK), was conducted to evaluate the efficacy and safety of Tecentriq compared with docetaxel in patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen. A total of 1225 patients were enrolled, with the primary analysis population consisting of the first 850 randomized patients. Eligible patients were stratified by PD-L1 expression status in tumor-infiltrating immune cells (IC), by the number of prior chemotherapy regimens, and by histology. Patients were randomized (1:1) to receive either Tecentriq or docetaxel. This study excluded patients who had a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Tumor assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter. Tumor specimens were evaluated prospectively for PD-L1 expression on tumor cells (TC) and IC and the results were used to define the PD-L1 expression subgroups for the analyses described below.

The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 64 years (range: 33 to 85), and 61% of patients were male. The majority of patients were white (70%). Approximately three-fourths of patients had non-squamous disease (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, 10% had CNS metastases at baseline, and most patients were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy five percent of patients received only one prior platinum-based therapeutic regimen.

Tecentriq was administered as a fixed dose of 1200 mg by IV infusion every 3 weeks. No dose reduction was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator. Docetaxel was administered 75 mg/m^2 by IV infusion on day 1 of each 21 day cycle until disease progression. For all treated patients, the median duration of treatment was 2.1 months for the docetaxel arm and 3.4 months for the Tecentriq arm.

The primary efficacy endpoint was OS. The key results of this study with a median survival follow-up of 21 months are summarized in Table 19. Kaplan-Meier curves for OS in the ITT population are presented in Figure 15. Figure 16 summarizes the results of OS in the ITT and PD-L1 subgroups, demonstrating OS in the ITT and PD-L1 subgroups, demonstrating OS benefit with Tecentriq in all subgroups, including those with PD-L1 expression <1% in TC and IC.

Table 19 Summary of Efficacy in the Primary Analysis Population (OAK)

Efficacy endpoints	TECENTRIQ	Docetaxel
Primary Efficacy Endpoint		
OS		
All comers*	n=425	n=425
No. of deaths (%)	271 (64%)	298 (70%)
Median time to events (months)	13.8	9.6
95% CI	(11.8, 15.7)	(8.6, 11.2)
Stratified‡ hazard ratio (95% CI)	0.73 (0.62, 0.87)	
p-value**	0.0003	
12-month OS (%)	218 (55%)	151 (41%)
18-month OS (%)	157 (40%)	98 (27%)
PD-L1 expression ≥ 1% in TC or IC	n=241	n=222
No. of deaths (%)	151 (63%)	149 (67%)
Median time to events (months)	15.7	10.3
95% CI	(12.6, 18.0)	(8.8, 12.0)
Stratified hazard ratio (95% CI)	0.74 (0.58, 0.93)	
p-value**	0.0102	
12-month OS (%)	58%	43%
18-month OS (%)	44%	29%
Secondary Endpoints		
Investigator-assessed PFS (RECIST v1.1)		
All comers*	n=425	n=425
No. of events (%)	380 (89%)	375 (88%)
Median duration of PFS (months)	2.8	4.0
95% CI	(2.6, 3.0)	(3.3, 4.2)
Stratified hazard ratio (95% CI)	0.95 (0.82, 1.10)	
Investigator-assessed ORR (RECIST v1.1)		
All comers	n=425	n=425
No. of responders (%)	58 (14%)	57 (13%)
95% CI	(10.5, 17.3)	(10.3, 17.0)
Investigator-assessed DOR (RECIST v1.1)		
All comers	n=58	n=57
Median in months	16.3	6.2
95% CI	(10.0, NE)	(4.9, 7.6)

CI=confidence interval; DOR=duration of response; IC=tumor-infiltrating immune cells; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1; TC = tumor cells.

* All comers refers to the primary analysis population consisting of the first 850 randomized patients

‡ Stratified by PD-L1 expression in tumor infiltrating immune cells, the number of prior chemotherapy regimens, and histology

** Based on the stratified log-rank test

Figure 15 Kaplan-Meier Plot for Overall Survival in the Primary Analysis Population (all comers) (OAK)

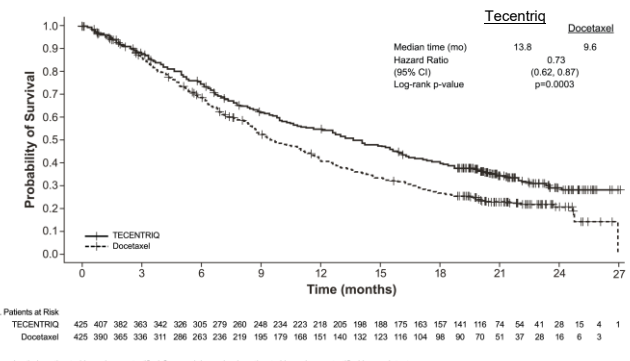
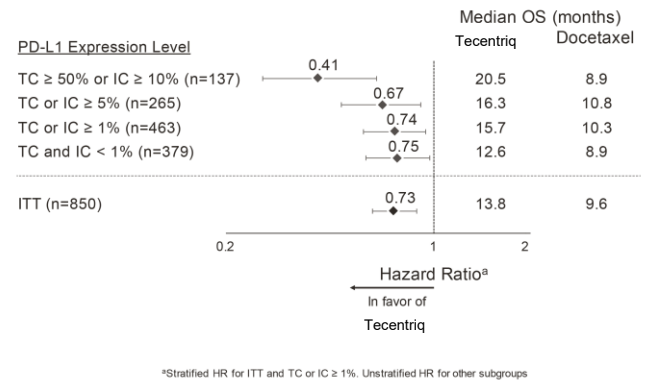


Figure 16 Forest Plot of Overall Survival by PD-L1 Expression in the Primary Analysis Population (OAK)



An improvement in OS was observed with Tecentriq compared to docetaxel in both non-squamous NSCLC patients (hazard ratio [HR] of 0.73, 95% CI: 0.60, 0.89; median OS of 15.6 vs. 11.2 months for Tecentriq and docetaxel, respectively) and squamous NSCLC patients (HR of 0.73, 95% CI: 0.54, 0.98; median OS of 8.9 vs. 7.7 months for Tecentriq and docetaxel, respectively). The observed OS improvement was consistently demonstrated across subgroups of patients including those with brain metastases at baseline (HR of 0.54, 95% CI: 0.31, 0.94; median OS of 20.1 vs. 11.9 months for Tecentriq and docetaxel respectively) and patients who were never smokers (HR of 0.71, 95% CI: 0.47, 1.08; median OS of 16.3 vs. 12.6 months for Tecentriq and docetaxel, respectively). However, patients with EGFR mutations did not show improved OS with Tecentriq compared to docetaxel (HR of 1.24, 95% CI: 0.71, 2.18; median OS of 10.5 vs. 16.2 months for Tecentriq and docetaxel respectively).

Prolonged time to deterioration of patient-reported pain in chest as measured by the EORTC QLQ-LC13 was observed with Tecentriq compared with docetaxel (HR 0.71, 95% CI: 0.49, 1.05; median not reached in either arm). The time to deterioration in other lung cancer symptoms (i.e. cough, dyspnea, and arm/shoulder pain) as measured by the EORTC QLQ-LC13 was similar between Tecentriq and docetaxel. The average global health status and functioning scores (i.e. physical, role, social, emotional, and cognitive) as measured by the EORTC QLQ-C30 did not show clinically meaningful deterioration over time for both treatment groups, suggesting maintained health-related quality of life and patient-reported functioning for patients remaining on treatment.

POPLAR

A phase II, multi-center, international, randomized, open-label, controlled study GO28753 (POPLAR), was conducted in patients with locally advanced or metastatic NSCLC. The primary efficacy outcome was overall survival. A total of 287 patients were randomized 1:1 to receive either Tecentriq or docetaxel. Randomization was stratified by PD-L1 expression status in IC, by the number of prior chemotherapy regimens and by histology. An updated analysis with a total of 200 deaths observed and a median survival follow-up of 22 months showed a median OS of 12.6 months in patients treated with TECENTRIQ, vs. 9.7 months in patients treated with docetaxel (HR of 0.69, 95% CI: 0.52, 0.92). ORR was 15.3% vs. 14.7% and median DOR was 18.6 months vs. 7.2 months for Tecentriq vs. docetaxel, respectively.

Tecentriq SC

IMscin001

A phase Ib/III, open-label, multi-center, international, randomized study, BP40657 (IMscin001), was conducted to evaluate the pharmacokinetics, efficacy and safety of Tecentriq SC compared with Tecentriq IV in patients with locally advanced or metastatic NSCLC who have not been exposed to cancer immunotherapy (CIT) and for whom prior platinum-based therapy has failed. IMscin001 was designed to demonstrate non-inferiority of the atezolizumab Cycle 1 (pre-dose Cycle 2) serum C_{trough} and model-predicted AUC from 0 to 21 days at Cycle 1 of atezolizumab SC compared with atezolizumab IV (co-primary endpoint). Secondary endpoints included efficacy [progression free survival (PFS), objective response rate (ORR), overall survival (OS), duration of response (DOR)], and patient-reported outcomes.

In Part 2 (Phase III), a total of 371 patients were enrolled and randomized to receive either 1875 mg of Tecentriq SC Q3W or 1200 mg of Tecentriq IV Q3W. No dose reduction was allowed.

Patients were excluded if they had a history of autoimmune disease; active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization.

The demographics and baseline disease characteristics were generally balanced between the treatment arms. The median age was 64 years (range: 27 to 85), and 69% of patients were male. The majority of patients were White (67%). Approximately two-thirds of patients (65%) had non-squamous disease, 5% had known EGFR mutation, 2% had known ALK rearrangements, 40% were PD-L1 positive (TC≥1% and/or IC≥1%), 16% had non-active CNS metastases at baseline, 26% had an ECOG PS of 0, 74% had an ECOG PS of 1, and most patients were current or previous smokers (70%). 80% received one prior therapeutic regimen.

Non-inferiority of the exposure from atezolizumab in Tecentriq SC compared to atezolizumab IV was demonstrated (see 3.2 Pharmacokinetic properties). Other key results are summarized below(see Table 20). At the time of primary analysis, the median follow-up was 4.7 months and OS and DOR results were immature. There were 86 (35%) deaths in the Tecentriq SC arm and 37 (30%) deaths in the intravenous atezolizumab arm.

Table 20 Summary of Efficacy from IMscin001

Efficacy endpoint	Tecentriq SC	Tecentriq IV
Investigator-assessed PFS (RECIST v1.1)*	n=247	n=124
No. of PFS events (%)	168 (68%)	84 (68%)
Median duration of PFS (months)	2.8	2.9
95% CI**	(2.1, 3.1)	(1.7, 4.2)
Investigator-assessed confirmed ORR (RECIST v1.1)*	n=245	n=124
No. of responders (%)	21 (8.6%)	10 (8.1%)
95% CI***	(5.4, 13)	(53.9, 14)

CI=confidence interval; ORR=objective response rate; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1

*descriptive analyses

**95% CI was calculated using the standard error derived from Greenwood's formula.

***95% CI for rate was constructed using the Clopper–Pearson method.

No clinically meaningful deterioration in the average health-related quality of life, role functioning, or physical functioning scores as measured by EORTC IL 57 was observed in the Tecentriq SC or Tecentriq IV arm, suggesting health-related quality of life and patient-reported functioning was maintained for patients remaining on treatment.

A post hoc updated analysis was performed 9 months after the primary analysis with a median survival follow-up of 9.5 months and mature OS results. The updated efficacy analysis results are summarized in Table 21.

Table 21: Summary of efficacy at updated analysis (IMscin001)

Efficacy endpoint	Tecentriq SC	Tecentriq IV
Investigator-assessed PFS (RECIST v1.1)*	n = 247	n = 124
No. of events (%)	219 (88.7%)	107 (86.3%)
Median (months) (95% CI)***	2.8 (2.7, 4.1)	2.9 (1.8, 4.2)
Investigator-assessed confirmed ORR (RECIST v1.1)*	n = 245	n = 124
No. of responders (%)	27 (11.0%)	13 (10.5%)
95% CI**	(7.39, 15.63)	(5.70,17.26)
OS*	n = 247	n = 124
No. of events (%)	144 (58.3%)	79 (63.7%)
Median (months) (95% CI)****	10.7 (8.5,13.8)	10.1 (7.5, 12.1)

CI = confidence interval; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors v1.1
* descriptive analyses
**95% CI was calculated using the standard error derived from Greenwood's formula.
***95% CI for rate was constructed using the Clopper–Pearson method.
**** 95% CI for rate was constructed using the Brookmeyer and Crowley method.

IMscin002

The IMscin002 study was a Phase II randomized, multi-center, open-label cross-over trial conducted in patients with non-small cell lung cancer (NSCLC) with the primary objective to evaluate patient preference for Tecentriq SC compared with Tecentriq IV. The 179 patients randomized in the study had either PD-L1-positive early-stage NSCLC and completed adjuvant treatment or were chemotherapy-naïve with high PD-L1 stage IV NSCLC. Following randomization, patients received 3 cycles of Tecentriq SC followed by 3 cycles of Tecentriq IV (Arm A) or 3 cycles of Tecentriq IV followed by 3 cycles of Tecentriq SC (Arm B).

Out of the 126 eligible patients, 123 (98%) completed the patient preference questionnaire (PPQ). At primary analysis, 87 out of 123 patients (71%) reported preferring subcutaneous administration of Tecentriq SC over Tecentriq IV and the main reason cited was that administration required less time in the clinic. Twenty-six out of 123 patients (21%) reported preferring Tecentriq IV over Tecentriq SC and the main reason cited was that it felt more comfortable during administration. Ten out of 123 patients (8%) had no preference for the route of administration.

Following the crossover periods, patients in both arms could continue treatment for up to 16 cycles (patients with early-stage NSCLC) or until disease progression or unacceptable toxicity (patients with stage IV NSCLC). Out of the 107 patients who entered the treatment continuation period, 85 (79%) patients (42 from IV/SC and 43 from SC/IV) chose to continue treatment with the SC route of administration.

The overall safety profile for all patients during the combined periods of Tecentriq IV and Tecentriq SC of the study was consistent with the established atezolizumab safety profile of IV and SC. No new or unexpected safety findings were observed and results were consistent with Tecentriq IV. Switching between Tecentriq SC and IV (and vice versa) was generally well tolerated and well-managed.

Overall, 77% of patients experienced at least one AE. During the crossover period, the proportion of patients who experienced AEs leading to treatment discontinuation/interruption were comparable between IV and SC administration.

1L TNBC

IMpassion130

A phase III, double-blind, two-arm, randomized, placebo-controlled study, WO29522 (IMpassion130), was conducted to evaluate the efficacy and safety of Tecentriq in combination with nab-paclitaxel, in patients with unresectable locally advanced or metastatic TNBC who had not received prior chemotherapy for metastatic disease. A total of 902 patients were enrolled and stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumor-infiltrating immune cells (IC) (PD-L1 stained tumour-infiltrating immune cells [IC] in <1% of the tumour area vs. ≥1% of the tumour area). Patients were randomized to receive Tecentriq (840 mg) or placebo IV infusions on Days 1 and 15 of every 28-day cycle, plus nab-paclitaxel (100 mg/m^2) administered via IV infusion on Days 1, 8 and 15 of every 28-day cycle. Patients received treatment until radiographic disease progression per RECIST v1.1, or unacceptable toxicity. Treatment with Tecentriq could be continued when nab-paclitaxel was stopped due to unacceptable toxicity.

Patients were excluded if they had a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; untreated or corticosteroid-dependent brain metastases. Tumor assessments were performed every 8 weeks (± 1 week) for the first 12 months after Cycle 1, day 1 and every 12 weeks (± 1 week) thereafter.

The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. Most patients were women (99.6%). Sixty-seven percent of patients were white (67.5%), 17.8% were Asian, 6.5% were Black or African American, and 4.4% were American Indian or Alaskan Native. The median age was 55 years (range: 20-86). Baseline ECOG performance status was 0 (58.4%) or 1 (41.3%). Overall, 41% of enrolled patients had PD-L1 expression ≥1%, 27% had liver metastases and 7% brain metastases at baseline. Approximately half the patients had received a taxane (51%) or anthracycline (54%) in the (neo) adjuvant setting. Patient demographics and baseline tumor disease in the PD-L1 expression ≥1% population were generally representative of the broader study population.

PFS, ORR and DOR results for patients with PD-L1 expression ≥1% with a median survival follow up of 13 months are summarized in Table 22 and Figure 17. In addition, PFS benefit was observed in subgroups.

A final OS analysis was performed in patients with PD-L1 expression ≥1% with a median follow-up of 19.12 months. OS results are presented in Table 22 and Figure 18.

Table 22 Summary of efficacy in patients with PD-L1 expression ≥1% IC (IMpassion130)

Key efficacy endpoints	Tecentriq + nab-paclitaxel	Placebo + nab-paclitaxel
Co-primary endpoints		
Investigator-assessed PFS (RECIST v1.1)	n=185	n=184
No. of events (%)	138 (74.6%)	157 (85.3%)
Median duration of PFS (months)	7.5	5.0
95% CI	(6.7, 9.2)	(3.8, 5.6)
Stratified hazard ratio‡ (95% CI)	0.62 (0.49, 0.78)	
p-value[1]	<0.0001	
12-month PFS (%)	29.1	16.4
OS	n=185	n=184
No. of deaths (%)	120 (64.9%)	139 (75.5%)
Median time to events (months)	25.4	17.9
95% CI	(19.6, 30.7)	(13.6, 20.3)
Stratified hazard ratio‡ (95% CI)	0.67 (0.53, 0.86)	
p-value[1,2]	0.0016	
Secondary endpoints		
Investigator-assessed ORR (RECIST 1.1)	n=185	n=183
No. of responders (%)	109 (58.9%)	78 (42.6%)
95% CI	(51.5, 66.1)	(35.4, 50.1)
No. of complete response (%)	19 (10.3%)	2 (1.1%)
No. of partial response (%)	90 (48.6%)	76 (41.5%)
No. of stable disease	38 (20.5%)	49 (26.8%)
Investigator-assessed DOR	n=109	n=78
Median in months	8.5	5.5
95% CI	(7.3, 9.7)	(3.7, 7.1)
Unstratified hazard ratio (95% CI)	0.60 (0.43, 0.86)	

1. Based on the stratified log-rank test
2. OS comparisons between treatment arms in patients with PD-L1 expression ≥1% were not formally tested, as per the pre-specified analysis hierarchy.

‡ Stratified by presence of liver metastases, and by prior taxane treatment
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1.; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival, NE=not estimable

Figure 17: Kaplan-Meier Plot for Progression Free Survival in patients with PD-L1 expression ≥1% IC (IMpassion130)

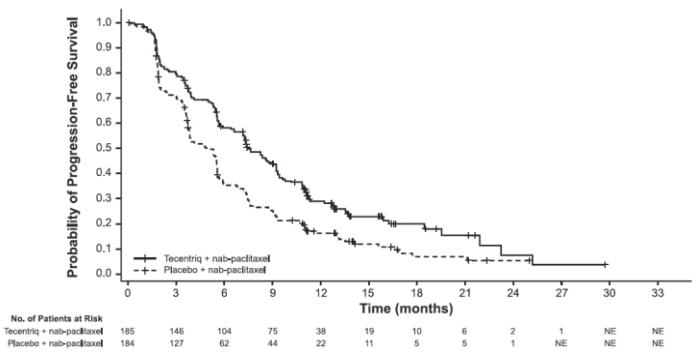
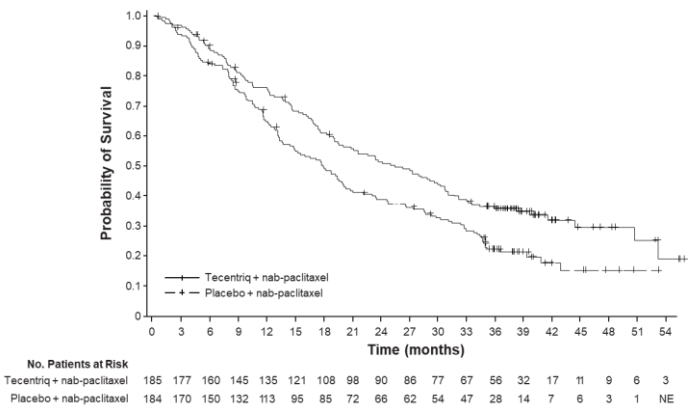


Figure 18: Kaplan-Meier Plot for Overall Survival in patients with PD-L1 expression ≥1% IC (IMpassion130)



Patient-reported endpoints measured by the EORTC QLQ-C30 suggest that patients maintained their global health status/health-related quality of life (HRQoL), physical functioning, and role functioning while on treatment. No differences in the time to a ≥10-point deterioration in HRQoL (HR: 0.94; 95% CI: 0.69, 1.28), physical function (HR: 1.02; 95% CI: 0.76, 1.37), or role function (HR: 0.77; 95% CI: 0.57, 1.04) were observed between the two arms. Mean scores at baseline for HRQoL (67.5 Tecentriq and nab-paclitaxel vs. 65.0 placebo and nab-paclitaxel), physical function (82.7 vs. 79.4), and role function (73.6 vs. 71.7) were comparable between arms; as well as throughout the course of treatment. In both arms, HRQoL, physical function and role function remained stable during treatment, with no clinically meaningful changes (a ≥10-point difference from baseline mean score) observed.

HCC

IMbrave150

A global phase III, randomized, multi-center, open-label study, YO40245 (IMbrave150), was conducted to evaluate the efficacy and safety of Tecentriq in combination with Avastin, in patients with locally advanced or metastatic and/or unresectable HCC, who have not received prior systemic treatment. A total of 501 patients were randomized (2:1) to receive either Tecentriq 1200 mg and 15 mg/kg of Avastin every 3 weeks administered via IV infusion, or sorafenib 400 mg orally twice per day. Randomization was stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), baseline AFP (<400 vs. ≥400 ng/mL) and ECOG performance status (0 vs. 1). Patients in both arms received treatment until loss of clinical benefit, or unacceptable toxicity. Patients could discontinue either Tecentriq or Avastin (e.g., due to adverse events) and continue on single-agent therapy until loss of clinical benefit or unacceptable toxicity associated with the single-agent.

The study enrolled adults who were Child-Pugh A, ECOG 0/1 and who had not received prior systemic treatment. Bleeding (including fatal events) is a known adverse reaction with Avastin and upper gastrointestinal bleeding is a common and life threatening complication in patients with HCC. Hence, patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding or high risk of bleeding. Patients were also excluded if they had moderate or severe ascites; history of hepatic encephalopathy; a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; untreated or corticosteroid-dependent brain metastases. Tumor assessments were performed every 6 weeks for the first 54 weeks following Cycle 1, Day 1, then every 9 weeks thereafter.

The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. The median age was 65 years (range: 26 to 88 years) and 83% were male. The majority of patients were Asian (57%) and white (35%). 40% were from Asia (excluding Japan), while 60% were from rest of world. Approximately 75% of patients presented with macrovascular invasion and/or extrahepatic spread and 37% had a baseline AFP ≥400 ng/mL. Baseline ECOG performance status was 0 (62%) or 1 (38%). The primary risk factors for the development of HCC were Hepatitis B virus infection in 48% of patients, Hepatitis C virus infection in 22% of patients, and non-viral disease in 31% of patients. HCC was categorized as Barcelona Clinic Liver Cancer (BCLC) stage C in 82% of patients, stage B in 16% of patients, and stage A in 3% of patients.

The co-primary efficacy endpoints were OS and IRF-assessed PFS according to RECIST v1.1. At the time of the primary analysis, patients had a median survival follow up time of 8.6 months. The data demonstrated a statistically significant improvement in OS and PFS as assessed by IRF per RECIST v1.1 with Tecentriq + Avastin compared to sorafenib. A statistically significant improvement was also observed in confirmed objective response rate (ORR) by IRF per RECIST v1.1 and HCC modified RECIST (mRECIST). The key efficacy results from the primary analysis are summarized in Table 23.

A descriptive updated efficacy analysis was performed with a median survival follow up time of 15.6 months. The key results from the updated analysis are summarized in Table 24. Kaplan-Meier curves for OS (updated analysis) and PFS (primary analysis) are presented in Figures 19 and 20, respectively.

Table 23 Summary of efficacy (IMbrave150 Primary Analysis)

Key efficacy endpoints	Tecentriq + Avastin		Sorafenib	
OS	n=336		n=165	
No. of deaths (%)	96 (28.6%)		65 (39.4%)	
Median time to event (months)	NE		13.2	
95% CI	(NE, NE)		(10.4, NE)	
Stratified hazard ratio‡ (95% CI)	0.58 (0.42, 0.79)			
p-value[1]	0.0006			
6-month OS (%)	84.8%		72.3%	
	RECIST v1.1		**HCC mRECIST**	
	Tecentriq + Avastin	Sorafenib	Tecentriq + Avastin	Sorafenib
IRF-assessed PFS	n=336	n=165	n=336	n=165
No. of events (%)	197 (58.6%)	109 (66.1%)	199 (59.2%)	111 (67.3%)
Median duration of PFS (months)	6.8	4.3	6.8	4.2
95% CI	(5.8, 8.3)	(4.0, 5.6)	(5.7, 7.7)	(4.0, 5.5)
Stratified hazard ratio‡ (95% CI)	0.59 (0.47, 0.76)		0.59 (0.46, 0.74)	
p-value[1]	<0.0001		N/A	
6-month PFS	54.5%	37.2%	54.3%	36.4%
IRF-assessed ORR	n=326	n=159	n=325	n=158
No. of confirmed responders (%)	89 (27.3%)	19 (11.9%)	108 (33.2%)	21 (13.3%)
95% CI	(22.5, 32.5)	(7.4, 18.0)	(28.1, 38.6)	(8.4, 19.6)
p-value[2]	<0.0001		<0.0001	
No. of complete responses (%)	18 (5.5%)	0	33 (10.2%)	3 (1.9%)
No. of partial responses (%)	71 (21.8%)	19 (11.9%)	75 (23.1%)	18 (11.4%)
No. of stable disease (%)	151 (46.3%)	69 (43.4%)	127 (39.1%)	66 (41.8%)
IRF-assessed DOR	n=89	n=19	n=108	n=21
Median in months	NE	6.3	NE	6.3
95% CI	(NE, NE)	(4.7, NE)	(NE, NE)	(4.9, NE)
6-month DOR (%)	87.6%	59.1%	82.3%	62.5%

‡ Stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL)
1. Based on stratified log-rank test
2. Based on stratified Cochran-Mantel-Haenszel test
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1; HCC mRECIST = Modified RECIST Assessment for Hepatocellular Carcinoma ; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival; NE=not estimable; N/A=not applicable

Table 24 Summary of efficacy (IMbrave150 Updated Analysis)

Key efficacy endpoints	Atezolizumab + Bevacizumab	Sorafenib
OS	n=336	n=165
No. of deaths (%)	180 (53.6%)	100 (60.6%)
Median time to event (months)	19.2	13.4
95% CI	(17.0, 23.7)	(11.4, 16.9)
Stratified hazard ratio‡ (95% CI)	0.66 (0.52, 0.85)	
IRF-assessed ORR, RECIST 1.1	n=326	n=159
No. of confirmed responders (%)*	97 (29.8%)	18 (11.3%)
95% CI	(24.8, 35.0)	(6.9, 17.3)
IRF-assessed DOR, RECIST 1.1	n=97	n=18
Median in months	18.1	14.9
95% CI	(14.6, NE)	(4.9, 17.0)

‡ Stratified by geographic region (Asia excluding Japan vs rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL)
* No. of complete responses (%): 25 (7.7%) in the atezolizumab + bevacizumab arm and 1 (0.6%) in the sorafenib arm
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1; CI=confidence interval; ORR=objective response rate; DOR=duration of respoe; OS=overall survival; NE=not estimable

Figure 19: Kaplan-Meier curve for Overall Survival (IMbrave150 Updated Analysis)

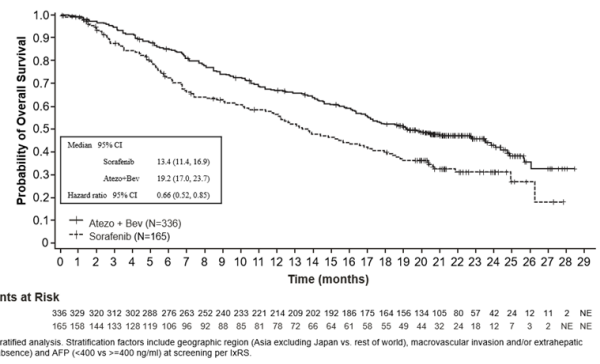
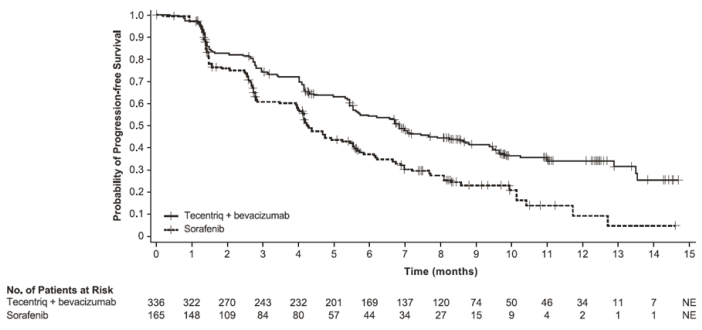


Figure 20 Kaplan-Meier Plot for Progression-Free Survival per RECIST v1.1 (IMbrave150 Primary Analysis)



The study evaluated patient-reported outcomes using the EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires. Time to deterioration (TTD) of patient-reported physical functioning, role functioning, and global health status/quality of life (GHS/QoL) on the EORTC QLQ-C30 were pre-specified secondary endpoints. TTD was defined as the time from randomization to the first deterioration (decrease from baseline of ≥10 points) maintained for two consecutive assessments, or one assessment followed by death from any cause within 3 weeks. Compared to sorafenib, the median TTD for patient-reported physical functioning was 13.1 vs. 4.9 months (HR 0.53, 95% CI 0.39, 0.73), 9.1 vs. 3.6 months (HR 0.62, 95% CI 0.46, 0.84) for role functioning and 11.2 vs. 3.6 months (HR 0.63, 95% CI 0.46, 0.85) for GHS/QoL. These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

GO30140
A global, open-label, multi-center, multi-arm Phase Ib study (GO30140) was also conducted in patients with solid tumors. Arm F of the study used a randomized design to evaluate the safety and efficacy of Tecentriq administered in combination with Avastin versus Tecentriq monotherapy in patients with advanced or metastatic and/or unresectable HCC who had not received prior systemic treatment. The primary efficacy endpoint was PFS assessed by IRF according to RECIST v1.1. A total of 119 patients were randomized 1:1 to receive either Tecentriq (1200 mg) and Avastin (15 mg/kg) by IV infusion every 3 weeks or Tecentriq (1200 mg) every 3 weeks. At the time of the primary analysis, the median survival follow up was 6.6 months. The combination of Tecentriq with Avastin showed statistically significant PFS benefit compared to Tecentriq monotherapy (HR of 0.55, 80% CI: 0.40, 0.74, p-value = 0.0108) with a median PFS of 5.6 months in patients treated with Tecentriq and Avastin, vs 3.4 months in patients treated with Tecentriq monotherapy.

3.1.3 Immunogenicity
As with all therapeutic proteins, there is the potential for immune response to atezolizumab. Across multiple phase III studies with intravenous atezolizumab, 13.1% to 36.4% of patients developed treatment-emergent anti-drug antibodies (ADAs) and 4.3% to 19.7% of patients developed neutralizing antibodies (NAbs). ADA and Nab status appeared to have no clinically relevant impact on atezolizumab pharmacokinetics, efficacy or safety.

In IMscin001, the incidence of treatment-emergent anti-atezolizumab antibodies in patients treated with Tecentriq SC and IV was 19.5% (43/221) and 13.9% (15/108), respectively. Anti-atezolizumab antibody status did not appear to have a clinically relevant impact on atezolizumab PK, efficacy or safety. The incidence of treatment-emergent anti-rHuPH20 antibodies in patients treated with Tecentriq SC was 5.4% (12/224). The clinical relevance of the development of anti-rHuPH20 antibodies after treatment with Tecentriq SC is unknown.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to Tecentriq with the incidence of antibodies to other products may be misleading.

3.2 PHARMACOKINETIC PROPERTIES
Tecentriq IV
The pharmacokinetics of atezolizumab have been characterized in patients in multiple clinical trials at doses 0.01 mg/kg to 20 mg/kg and 1200mg every 3 weeks, as well as 840mg every 2 weeks. Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg. A population analysis that included 472 patients described atezolizumab pharmacokinetics for the dose range: 1- 20 mg/kg with a linear two-compartment disposition model with first-order elimination. Based on pharmacokinetic modeling, the overall exposure of atezolizumab administered at doses of 840 mg every 2 weeks, 1200 mg every 3 weeks and 1680mg every 4 weeks are comparable. A population pharmacokinetic analysis suggests that steady-state is obtained after 6 to 9 weeks after multiple doses. The maximum systemic accumulation ratio across dosing regimens is 3.3.
Based on an analysis of exposure, safety and efficacy data, the following factors have no clinically relevant effect: age (21-89 years), body weight, gender, positive ADA status, albumin levels, tumor burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status.

Tecentriq SC
Atezolizumab model-predicted exposure metrics following Tecentriq SC (1875 mg Q3W SC) and intravenous atezolizumab (1200 mg Q3W IV) administration in the IMscin001 study are shown in Table 22.

Atezolizumab Cycle 1 observed serum C_{trough} (i.e., pre-dose cycle 2) showed non-inferiority of atezolizumab within Tecentriq SC to intravenous atezolizumab, with a geometric mean ratio (GMR) of 1.05 (90% CI: 0.88–1.24).

The GMR for Cycle 1 model-predicted for AUC from 0 to 21 days ($AUC_{0\text{-}21d}$) was 0.87 (90% CI: 0.83–0.92). The pre-specified non-inferiority margin for Cycle 1 observed serum C_{trough} and Cycle 1 model-predicted $AUC_{0\text{-}21d}$ is 0.8.

The maximum systemic accumulation ratio following 1875 mg Q3W of Tecentriq SC is 2.2.

The model-predicted C_{trough} and AUC at steady state were comparable for Tecentriq SC and intravenous atezolizumab (see Table 25).

Table 25 Atezolizumab steady state exposure (median with 5th-95th Percentiles) following subcutaneous or intravenous administration of atezolizumab

Parameter	Atezolizumab within Tecentriq SC	Intravenous Atezolizumab
C_{trough} at steady state[a] (mcg/mL)	205 (70.3-427)	179 (98.4-313)
AUC at steady state[a] (mcg/mL•day)	6163 (2561-11340)	6107 (3890-9334)

a) Model predicted exposure based on population pharmacokinetics analysis

3.2.1 Absorption
Tecentriq IV is administered as an IV infusion.

Tecentriq SC
Based on population PK analysis, the absolute bioavailability was 72% with coefficient of variation (CV%) of 83% and the first-order absorption rate (K_a) is 0.3 (1/day). The atezolizumab geometric mean maximum serum concentration (C_{max}) was 189 mcg/mL and median time to maximum serum concentration (T_{max}) was 4.5 days (median; 2.2-9.0 days min-max).

3.2.2 Distribution
A population pharmacokinetic analysis indicates that central compartment volume of distribution (V1) is 3.28 L and volume at steady-state (Vss) is 6.91 L in the typical patient.

3.2.3 Metabolism
The metabolism of Tecentriq has not been directly studied. Antibodies are cleared principally by catabolism.

3.2.4 Elimination
A population pharmacokinetic analysis indicates that the clearance of atezolizumab is 0.200 L/day and the typical terminal elimination half-life ($t_{1/2}$) is 27 days.

3.2.5 Pharmacokinetics in Special Populations
Pediatric Population
Tecentriq IV
The pharmacokinetic results from one early-phase, multi-centre open-label study that was conducted in pediatric (<18 years, n=69) and young adult patients (18-30 years, n=18), show that the clearance and volume of distribution of atezolizumab were comparable between pediatric patients receiving 15 mg/kg and young adult patients receiving 1200 mg of atezolizumab every 3 weeks when normalized by body weight, with exposure trending lower in pediatric patients as body weight decreased. These differences were not associated with a decrease in atezolizumab concentrations below the therapeutic target exposure. Data for children <2 years is limited thus no definitive conclusions can be made.

Tecentriq SC
No dedicated studies of Tecentriq SC have been conducted in pediatric patients.

Geriatric Population
No dedicated studies of Tecentriq have been conducted in geriatric patients. The effect of age on the pharmacokinetics of atezolizumab was assessed in a population pharmacokinetic analysis. Age was not identified as a significant covariate influencing intravenous atezolizumab pharmacokinetics based on patients of age range of 21-89 years (n = 472), and median of 62 years of age. No clinically important difference was observed in the pharmacokinetics of subcutaneous or intravenous atezolizumab among patients < 65 years (n = 138 for SC or n = 274 for IV), patients between 65-75 years (n = 89 for SC or n = 152 for IV) and patients > 75 years (n = 19 for SC or n = 46 for IV) (see section 2.2.1 Special Dosage Instructions).

Renal impairment
No dedicated studies of Tecentriq have been conducted in patients with renal impairment. In the population pharmacokinetic analysis, no clinically important differences in the clearance of intravenous atezolizumab were found in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n = 208) or moderate (eGFR 30 to 59 mL/min/1.73 m^2; n = 116) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m^2; n = 140) renal function. Only a few patients had severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2; n = 8) (see section 2.2.1 Special Dosage Instructions).

No clinically relevant differences in the pharmacokinetics of subcutaneous atezolizumab were found in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n=111) or moderate (eGFR 30 to 59 mL/min/1.73 m^2; n=32) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m^2; n=103) renal function.

Hepatic impairment
No dedicated studies of Tecentriq have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of intravenous or subcutaneously administered atezolizumab between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 x ULN and any AST, or moderate hepatic impairment (bilirubin >1.5 to 3x ULN and any AST). No data are available in patients with severe (bilirubin > 3.0 x ULN and any AST) hepatic impairment. Hepatic impairment was defined by the National Cancer Institute (NCI) criteria of hepatic dysfunction (see section 2.2.1 Special Dosage Instructions).

3.3 NONCLINICAL SAFETY
3.3.1 Carcinogenicity
No carcinogenicity studies have been conducted with Tecentriq.

3.3.2 Genotoxicity
No genotoxicity studies have been conducted with Tecentriq.

3.3.3 Impairment of Fertility
No fertility studies have been conducted with Tecentriq; however assessment of the cynomolgus monkey male and female reproductive organs was included in the chronic toxicity study. Tecentriq had an effect on menstrual cycles in all female monkeys in the 50 mg/kg dose group characterized by an irregular cycle pattern during the dosing phase and correlated with the lack of fresh corpora lutea in the ovaries at the terminal necropsy; this effect was reversible during the dose-free recovery period. There was no effect on the male reproductive organs.

3.3.4 Reproductive Toxicity
No reproductive or teratogenicity studies in animals have been conducted with Tecentriq. The PD-L1/PD-1 signaling pathway is well established as essential in maternal / fetal tolerance and embryo-fetal survival during gestation. Administration of Tecentriq is expected to have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo lethality.

3.3.5 Other
Subcutaneous formulation
No carcinogenicity, genotoxicity, or fertility studies were conducted for recombinant human hyaluronidase. Reproductive toxicology studies with rHuPH20 revealed embryofetal toxicity in mice at high systemic exposure, but did not show teratogenic potential.

4. PHARMACEUTICAL PARTICULARS
4.1 STORAGE
Tecentriq IV
Vials
Store at 2°C-8°C.
Tecentriq should be protected from light.
Do not freeze. Do not shake.

Shelf life
This medicine should not be used after the expiry date (EXP) shown on the pack.
The diluted solution for infusion should be used immediately. If the solution is not used immediately, it can be stored for up to 24 hours at 2°C-8°C, or 8 hours at ambient temperature (≤ 25°C).

Tecentriq SC
Vials
Store at 2°C-8°C.
Keep vial in outer carton in order to protect from light.
Do not freeze. Do not shake.

Shelf life
As registered locally.
This medicine should not be used after the expiry date (EXP) shown on the pack.

Storage of the syringe
- From a microbiological point of view, the product should be used immediately once transferred from the vial to the syringe since the medicine does not contain any antimicrobial-preservative. If not used immediately, in-use storage times and conditions prior to use are the responsiblity of the user and normally not longer than 24 hours at 2°C to 8°C, unless preparation has taken place under controlled and validated aseptic conditions.
- The closed syringe can be stored at ≤30°C (86°F) for up to 8 hours in diffuse daylight and in the refrigerator [2°C to 8°C (36°F to 46°F)] for up to 30 days.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL
Tecentriq IV
Instructions for dilution
Tecentriq should be prepared by a healthcare professional using aseptic technique. Use sterile needle and syringe to prepare Tecentriq. Withdraw the required volume of Tecentriq liquid concentrate from the vial and dilute into the required PVC, polyethylene (PE) or polyolefin infusion bag containing 0.9% sodium chloride solution. Dilute with 0.9% Sodium Chloride Injection only. After dilution, the final concentration of the diluted solution should be between 3.2 and 16.8 mg/mL. The bag should be gently inverted to mix the solution in order to avoid foaming. Once the infusion is prepared it should be administered immediately. (See section 4.1 Storage).
This medicinal product must not be mixed with other medicinal products.
No preservative is used in Tecentriq therefore each vial is for single use only. Discard any unused portion.

Incompatibilities
No incompatibilities have been observed between Tecentriq and IV bags with product-contacting surfaces of polyvinyl chloride (PVC), polyolefin bags, polyethylene (PE) or polypropylene (PP). In addition, no incompatibilities have been observed with in-line filter membranes composed of polyethersulfone or polysulfone, and infusion sets and other infusion aids composed of PVC, PE, polybutadiene, or polyetherurethane.

Tecentriq SC
Tecentriq SC is a ready-to-use solution for subcutaneous injection only and should not be diluted mixed with other drugs.
Tecentriq SC should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.
Tecentriq solution for injection is for single use only and should be prepared by a healthcare professional.

Preparation of the Syringe
Tecentriq SC does not contain any antimicrobial preservative. If the dose is not administered immediately, refer to "Storage of the Syringe" below.
Prior to use, remove the vial from refrigerated storage and allow the solution to come to room temperature.
Withdraw the entire contents of Tecentriq SC solution from the vial with a syringe and transfer needle (18G recommended).
Remove the transfer needle and attach a SC infusion set (e.g. winged / butterfly) containing a 23-25G stainless steel needle for injection. Use a SC infusion set with residual hold-up volume NOT exceeding 0.5 mL for administration.
Prime the SC infusion line with the drug product solution to eliminate the air in the infusion line and stop before the fluid reaches the needle.
Ensure the syringe contains exactly 15 mL of drug product solution after priming and expelling any excess volume from the syringe.
Administer immediately to avoid needle clogging. DO NOT store the prepared syringe that has been attached to the already-primed infusion set.

Storage of the syringe
If the dose is not used immediately, use aseptic technique to withdraw the entire contents of Tecentriq SC solution from the vial into the syringe to account for the dose volume (15mL) plus the priming volume for the SC infusion set. Replace the transfer needle with a syringe closing cap. DO NOT attach a SC infusion set for storage.
If the syringe was stored in a refrigerator, allow the syringe to reach room temperature prior to administration.

Incompatibilities
No incompatibilities have been observed between Tecentriq SC and polypropylene (PP), polycarbondate (PC), stainless steel (ss), polyvinyl chloride (PVC), and polyurethanes (PU).

Tecentriq IV and SC
Disposal of unused / expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

4.3 PACKS
Tecentriq IV
Vial 1200 mg/ 20 ml 1
Vial 840mg/ 14 ml 1

Tecentriq SC
Vial 1875mg/ 15ml 1

Medicine: keep out of reach of children

Current at December 2025

Roche F. Hoffmann-La Roche Ltd, Basel, Switzerland